Comparative effectiveness of natural and synthetic bone grafts in oral and maxillofacial surgery prior to insertion of dental implants: Systematic review and network meta-analysis of parallel and cluster randomized controlled trials

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Abstract: OBJECTIVES Bone grafts are often used to enhance bone volume/quality prior to implantation insertion. This systematic review compares the histomorphometric effectiveness of bone grafts in an evidence-based manner. DATA Randomized clinical trials comparing histomorphometrically the % of newly-formed bone between two grafts were included. Risk of bias within and across studies was assessed with the Cochrane tool and the GRADE approach, respectively. Random-effects pairwise meta-analyses were conducted, followed by network meta-analysis, network meta-regression and sensitivity analyses. SOURCES Four electronic databases were searched from inception to June 2015 without limitations. STUDY SELECTION A total of 12 trials (5 parallel; 7 cluster) with a total of 231 patients (302 grafted sites) were included. No statistically significant differences were found in the % of new bone from pairwise comparisons between any two bone grafts. Treatment ranking based on the evidence network indicated that autografts presented the highest percentage of new bone, followed by synthetic grafts, xenografts, and allografts. No differences according to patient age, sex, healing time, membrane used or kind of surgical graft use were identified. Our confidence on pairwise comparisons was moderate to very low due to study limitations, inconsistency, and imprecision; our confidence on graft ranking was moderate due to study limitations. CONCLUSIONS No significant differences were found in the percentage of new bone between any two grafts. CLINICAL SIGNIFICANCE Synthetic bone substitutes or xenologous bone grafts can be used as an alternative to autologous graft in order to overcome problems of additional surgeries or limited graft availability.

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Title Page

Comparative effectiveness of natural and synthetic bone grafts in oral and maxillofacial surgery prior to insertion of dental implants: systematic review and network meta-analysis of parallel and cluster randomized controlled trials

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A B S T R A C T

Objectives: Bone grafts are often used to enhance bone volume / quality prior to implantation insertion. This systematic review compares the histomorphometric effectiveness of bone grafts in an evidence-based manner.

Data: Randomized clinical trials comparing histomorphometrically the % of newly-formed bone between two grafts were included. Risk of bias within and across studies was assessed with the Cochrane tool and the GRADE approach, respectively. Random-effects pairwise meta-analyses were conducted, followed by network meta-analysis, network meta-regression and sensitivity analyses.

Sources: Four electronic databases were searched from inception to June 2015 without limitations.

Study selection: A total of 12 trials (5 parallel; 7 cluster) with a total of 231 patients (302 grafted sites) were included. No statistically significant differences were found in the % of new bone from pairwise comparisons between any two bone grafts. Treatment ranking based on the evidence network indicated that autografts presented the highest % of new bone, followed by synthetic grafts, xenografts, and allografts. No differences according to patient age, sex, healing time, membrane used or kind of surgical graft use were identified. Our confidence on pairwise comparisons was moderate to very low, due to study limitations, inconsistency, and imprecision; our confidence on graft ranking was moderate, due to study limitations.

Conclusions: No significant differences were found in the % of new bone between any two grafts.

Clinical significance: Synthetic bone substitutes or xenologous bone grafts can be used as an alternative to autologous graft, in order to overcome problems of additional surgeries or limited graft availability.

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1. Introduction

1.1. Background

Resorption of the edentulous or partially edentulous alveolar ridge frequently compromises dental implant placement in a prosthetically ideal position. Therefore, augmentation of an insufficient bone volume is often indicated prior to or in conjunction with implant placement to attain predictable long-term functioning and an esthetic treatment outcome. Autogenous bone grafts (AUTs) are considered the gold standard in bone regeneration procedures [1]. However, donor site morbidity, transmission of live viruses, unpredictable resorption, limited quantities available, and the need to include additional surgical sites are autografts-related drawbacks that have intensified the search for suitable alternatives [2].

Bone-substitute materials have increased in popularity as adjuncts to or replacements for AUTs in bone augmentation procedures to overcome many of their limitations [3]. Bone-substitute materials can be categorized in three groups: (1) allogenic grafts (ALLs), from another individual within the same species; (2) xenogenic grafts (XENs), from another species; or (3) alloplastic, synthetically produced grafts (SYNs). According to contemporary trends, the ideal characteristics of a bone-substitute material include space maintenance, pre-specification of the desired anatomical form, support to the periosteum, acceleration of bone remodeling, osteoconductive guidance, carrier function for antibiotics, growth factors or gene therapy approaches or scaffolds for tissue engineering [2,4-6]. It may be too optimistic to expect that a single grafting material fulfill all these functions and will be suitable for all indications.

A large number of systematic reviews with meta-analyses has been published in the last five years [7-15], but most were of suboptimal conduct or reporting and / or had methodological limitations [16], while none performed network meta-analysis to compare directly all existing bone graft alternatives.

1.2. Objective

We conducted a systematic review of parallel and cluster randomized trials (RCTs) including network meta-analysis in order to investigate the comparative effectiveness of bone grafts used in oral and

maxillofacial surgery prior to implant placement in humans and to compare all grafts with the current gold standard (AUT).

2. Materials and Methods

2.1. Protocol and registration

The protocol for this review was made a priori based on the PRISMA-P statement [17], registered in PROSPERO (CRD42015023467), and all *post hoc* changes were noted. This systematic review was conducted according to Cochrane Handbook [18] and reported according to the newly-published PRISMA Extension for network meta-analyses [19].

2.2. Eligibility criteria and literature search

RCTs on human patients comparing any two natural or synthetic bone grafts were included. No lumping of interventions was performed during the study selection phase. Non-RCTs were excluded, due to bias [20-23]. Both parallel (one graft per patient) and clustered trials (>one graft per patient) were included and assessed appropriately together, by calculating for the latter clustering-adjusted estimates through random-effects regression. The pre-specified eligibiligy criteria can be found in Appendix 1.

Four electronic databases were searched systematically by one author (SNP) without any limitations from inception up to June 15th, 2015 and re-checked in October 2015 for manual additions (Appendix 1). Four additional sources (Scopus, Google Scholar, ClinicalTrials.gov, and ISRCTN registry) were manually searched for additions. Authors contacted for missing data were asked about additional missed trials. No search limitations concerning language, publication year or status were applied, except for studies on humans, where available. The reference/citation lists of the included trials and relevant systematic reviews were manually searched as well.

2.3. Study selection

Titles identified were screened by one author (SNP) with a subsequent duplicate independent checking of their abstracts/full-texts against the eligibility criteria by two authors (SNP, PNP), while conflicts were resolved by a third author (JD).

2.4. Data collection

Characteristics of included trials and numerical data were extracted in triplicate by three authors (SNP, PNP, JD) using *a priori* constructed and piloted extraction forms. Lumping of identified grafts was performed into four categories: AUT, ALL, SYN, and XEN. In case of combinations of grafts, the graft was categorized according to the graft with over 70% contribution (Appendix 1). Piloting of the forms was performed during the protocol stage until over 90% agreement was reached. Missing or unclear information was requested per e-mail by the trials' authors.

2.5. Risk of bias in individual trials

The risk of bias of the included trials was assessed using Cochrane's risk of bias tool [18] after initial calibration by three review authors (SNP, PNP, JD) and any disagreement was discussed with a fourth author (WG). The risk of bias assessment for each trial was based on the primary outcome (% new bone) or, if this was not included in the trial, on the trial's primary outcome. The risk of bias was incorporated in data synthesis using the framework of Salanti *et al*. [24].

2.6. Data synthesis

As the outcome of bone augmentation could be influenced by the bone graft, the technique, the patient's individual biological response, and post-operative management, a random-effects model according to DerSimonian and Laird was deemed appropriate to incorporate this variability [25]. Both pairwise and network meta-analyses were conducted to obtain estimates for primary and secondary outcomes, and presented as Mean Differences (MDs) or Relative Risks (RRs) with 95% Confidence Intervals (CIs). Heterogeneity was conventionally assessed with tau^2 and I^2 (Appendix 2) and 95% Prediction Intervals (PrIs) were calculated to predict effects in a future clinical setting by incorporating heterogeneity. For clustered trials, the raw data were requested from the trial's authors and clustering-adjusted estimates were calculated with univariable and multivariable regression.

The results of all direct and mixed comparisons were presented in league tables and forest plots. The latter were augmented with contours of effect magnitude based on multiples of the mean standard deviation of the included outcome (10%): 0-10% - clinically-irrelevant effect, 10%-20% - moderate effect, 20%-30% - large effect, and >30% - very large effect. In order to rank treatments for an outcome, the Surface Under the Cumulative RAnking (SUCRA) probabilities were used, which express as a percentage the effectiveness of every intervention relative to an imaginary intervention that is always the best

without uncertainty [26,27]. Thus, large SUCRA scores indicate a more effective intervention. All analyses were done with Stata version 13 (StataCorp, College Station, TX) by one author (SNP), with the commands xtgee, metan, mvmeta, network and the routines from Chaimani *et al*. [28]. A two-tailed P-value of 0.05 was considered significant for hypothesis-testing.

The following pre-specified effect modifiers were checked as possible sources of inconsistency / heterogeneity at patient or study level with conventional methods (Appendix 2): (a) characteristics of patients (age, gender), (b) type of graft, (c) surgical procedure conducted, (d) use of membrane, (e) membrane type, and (f) healing time.

2.7. Risk of bias across studies

The overall quality of clinical recommendations (confidence in effect estimates) for each of the main outcomes and for the network was rated using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach, based on the proposal of Salanti *et al*. [24]. For this assessment, the risk of bias of each included trial was re-assessed separately at outcome level. The GRADE assessment was performed by one author (SNP) and discussed with the rest (PNP, JD, WG).

2.8. Additional analyses

Signs of publication bias were planned to be assessed, if ten or more included studies contributed to an outcome, with a 'comparison-adjusted' funnel plot together with an accompanying statistical test [28]; this was not performed, as no appropriate treatment ordering by bias-related factors was possible. Small-study effects were assessed by network meta-regression according to trial size (effect variance).

Sensitivity analyses were conducted (i) by attempting to form an alternate network geometry and to compare its results, (ii) comparing the design-by-treatment model to the original analysis, and (iii) examining the basic design of the included studies and its influence.

3. Results

3.1. Study selection

The systematic electronic and manual search identified 283 and 7 reports, respectively (Fig 1). From these a total of 104 and 167 reports were excluded through screening and fulltext assessment,

respectively (Appendix 3). Finally, a total of 45 papers (pertaining to 41 unique trials) were included in the systematic review.

3.2. Study characteristics

The characteristics of the trials included in the qualitative part of this study (i.e. systematic review) can be seen in Appendices 4-6. From the 41 included trials 6 (15%) were multicenter and 37 (90%) took place in a university environment from 15 different countries. A total of 852 patients (47% male and 53% female) were included with an average of 20.8 patients per trial and an average age of 50.6 years. From the included trials, 17 (41%) were of parallel design and 24 (59%) of clustered design (i.e. more than one grafted site per patient).

As far as surgical procedures were concerned, 54% of the trials assessed sinus lift, 32% preservation of extraction sockets, 12% ridge augmentation, and the last 2% both ridge augmentation and sinus lift with a total of 1164 surgical sites being grafted. A wide variety of bone grafts were used, which were categorized as AUT (harvested mostly intraorally or from the iliac crest), ALL, SYN (based on hydroxyapatite or calcium sulphate), and XEN (mostly represented by Bio-Oss; Geistlich, Wolhusen, Switzerland). The grafted region was covered additionally by a membrane (mostly collagen ones) in 56% of the trials, by a collagen sponge or fibrin glue in 4% of the trials or without additional means in 37% of the trials.

In all trials that assessed histomorphometrically the grafted regions, bone samples were collected after a healing phase of 3-9 months during a subsequent implant insertion. Among the 25 out of 41 included trials that adequately reported the subsequent implant insertion, a total of 1261 implants were inserted (mean of 50.4 implants per study).

3.3. Risk of bias within studies

The risk of bias assessment for the 41 included trials can be seen in Appendices 7-9. High risk of bias arising from problematic generation of the random sequence was seen in 10% of the trials, bias from incomplete outcome data in 7% of the trials, and bias from selective outcome reporting in 5% of the trials. The main source of bias however, was residual bias due to other reasons, including poor trial design, inadequate data handling for cluster trials or failing to take into account confounding introduced from smoking or systemic diseases. It is however important, that extreme uncertainty exists on the bias

assessment of random sequence generation, allocation concealment and blinding, as these were very poorly reported, making a formal assessment of their appropriateness impossible ("unclear" categories in the risk of bias summary).

3.4. Results of individual trials

The results of the 41 individual trials that were included in the systematic review are expressed as MDs or RRs in Appendix 10. In the case of available individual patient data, these are based on univariable or multivariable generalized estimating equations accounting for clustering within patients and any possible confounders reported in the original trial (patient sex, age, healing time, membrane type).

3.5. Network structure and synthesis of results

Out of the 41 trials included in the qualitative part of this study (i.e. systematic review), only 12 were included in the quantitative synthesis (i.e. meta-analyses) for various reasons (Fig 1). These pertained to 5 pairwise comparisons (AUT vs ALL, AUT vs SYN, AUT vs XEN, ALL vs SYN, and SYN vs XEN), with most of them being statistically insignificant, although high heterogeneity was found (Table 1; Appendix 11).

When assessing all comparisons for the primary outcome of the review (% of new bone) at the same time, a square network of 12 trials, 231 patients and 302 grafted sites was formed (Fig 2). This network included the 5 above-mentioned direct comparisons, 1 indirect comparison (ALL vs XEN), and additional mixed-treatment information from the whole network (Appendix 12). The assumption of transitivity was satisfied on theoretical grounds, as all trials randomized adult patients of similar age and sex, and with similar medical background, as the primary outcome measurement pre-included the ability to subsequently insert a dental implant. No major violation of transitivity was identified on practical ground, as mean ages and the % of sex distribution was relatively similar among all comparisons (Appendix 13). The results for all comparisons arising from direct comparisons and from the evidence network can be seen in Fig 3 and Appendix 14. All other grafts resulted in lower % of new bone compared to AUT, while both SYN and XEN resulted in higher % of new bone compared to ALL. Finally, SYN resulted in slightly higher % of new bone compared to XEN, although high heterogeneity existed (tau^2 of 141.37) and all abovementioned comparisons were statistically non-significant, due to small sample size and wide 95% CIs. The ranking of the various grafts according to the % of new bone formed is found in Fig 4. As can be seen from the SUCRA plots, AUT had the best results, followed by SYN, XEN, and finally ALL.

3.6. Exploration of inconsistency

When inconsistency was checked in a loop-specific approach (Appendix 15), one of the two existing closed triangular was inconsistent. Additionally, comparison of direct and indirect estimates (node-splitting procedure) indicated considerable differences for four out of five comparisons, which were almost statistically significant at 5%, despite the very wide confidence intervals, due to the limited number of trials (Appendix 16). Data were double-checked and we could not identify any important variable that differed across comparisons/loops. However, the number of included studies in all loops was typically small, so the extent of inconsistency was not deemed substantial enough. Additionally, the comparison of the original analysis (consistency model) with the inconsistency model yielded similar results (Appendix 17).

3.7. Risk of bias across studies

Our confidence in the evidence according to the GRADE approach can be found in Table 2 and Appendix 18-19. As can be seen, our confidence in pairwise comparisons was moderate to very low, mainly due to study limitations, inconsistency, and imprecision. On the other side, confidence in the overall ranking of treatments was found to be moderate, due to inherent limitations of the included studies.

3.8. Additional analyses (alternate geometry, subgroup analysis, meta-regression)

As an additional analysis, we attempted to construct an alternative geometry network by analyzing all commercially available SYNs separately (Appendix 20). This resulted however in a markedly inconsistent network with sparse connections, which made inferences about the network's transitivity and coherence void. Under this alternate treatment ranking (Appendix 21), AUT was the worst graft in terms of % of new bone, which is highly improbable based on direct estimates. Therefore, the analysis of this alternate network geometry was discarded as instable.

The effect of the various confounding covariates (patient sex, patient age, type of membrane, and healing time) from individual patient data can be seen in Appendix 22. After calculating the effect of each covariate on the primary outcome within-trials from raw data, and pooling across-trials, no significant modifying effect could be found ($P>0.05$). The single exception was the type of membrane used over the

graft, where the expanded polytetrafluoroethylene membrane was associated with lower % of new bone compared to the acellular dermal matrix allograft membrane (P=0.040).

Network meta-regression was undertaken in order to address the impact of possible confounders on the network in a universal scale. As can be seen in Appendix 17, the model fit was not influenced by surgery type (socket preservetation, sinus lift or combination procedures), but was affected by the use of membranes over the grafts. However, treatment rankings based on the original analysis or on analysis adjusting for use of membrane (or not) for the primary and secondary outcomes studied were almost exactly the same. The slight variation in the treatment ranking regarding % of new bone was discarded as non-credible, as it contradicted with direct evidence of AUT's superiority, and therefore, the modifying effect of membrane use was deemed insignificant.

3.9. Secondary outcomes

A large number of outcomes were reported from the included studies (Appendix 10), which are however only briefly discussed, as they did not refer to histomorphometry and therefore were not the main focus of this review.

As far as secondary histomorphometry outcomes are concerned, many trials also reported the % residual graft particles and the % connective tissue from the samples harvested prior to implant insertion (Appendix 23). The evidence network and the contribution plots (Appendices 24-25) for these two outcomes was similar to the network for the primary outcome (% of new bone). Both networks for the % residual graft particles and the % connective tissue presented considerable heterogeneity (tau^2 of 106.30 and 73.62), respectively. AUT and XEN were ranked as equally probable to be the best grafts in terms of having the least % of residual graft particles, while AUT and ALL were equally probable to be the be in terms of % of connective tissue (Appendix 26). However, the ranking in places 2-3 was SYN-ALL and XEN-SYN for % of residual graft and % of connective tissue, respectively. When the primary outcome of % new bone and the secondary outcome of % residual graft were taken into account at the same time in a clustered ranking plot (Appendix 27), AUT was the best graft, while SYN and XEN were relatively comparable in terms of effectiveness, and ALL was the worst. Finally, node-splitting analysis regarding these two secondary outcomes (Appendix 28) did not identify any serious threats to consistency, although wide confidence intervals were present.

4. Discussion

4.1. Summary of evidence

This systematic review assessed in an evidence-based matter the histomorphometric effects of various bone grafts in sinus lift, extraction socket preservation, and ridge augmentation in human patients prior to the insertion of dental implants. Using a network meta-analysis approach, no statistically significant differences could be found for most of the histomorphometric outcomes, although this was probably due to few included studies and subsequently wide CIs. Based on the evidence network, it could be shown that AUTs is the gold standard both in terms of new bone formation and graft integration, which agrees with existing knowledge [1]. The same clear distinction could be made for ALL, which was the worst graft family studied for both bone formation and graft resorption. As far as SYN and XEN are concerned, they formed an intermediate category, where SYN was associated with higher bone formation and lower graft resorption, while the opposite was found for XEN.

SYNs used in oral and maxillofacial surgery have been reported to be bioabsorbable and non-toxic [29] with a chemical structure similar to bone mineral composition. Previous studies have reported that osteoclast-like cells (or foreign body giant cells [30]) can be observed both along the surface of newly-formed bone and directly on the graft granules during the healing phase [31-35]. Additionally, certain SYNs (bioactive glasses) have been reported to become coated by a calcium-phospate layer *in vivo* and to form a direct chemical bond to bone [29]. Certain modern XENs in the nanometer range like Ostim (Heraeus Kulzer GmbH, Hanau, Germany) or NanoBone (Artoss GmbH, Rostock Germany) might also lead to a significant increase in contact surface area and thereby result in augmented new bone regeneration [36,37]. The single identified trial however, that directly compared Ostim to another SYN (SINTLife, FinCeramica, Faenza, Italy) did not find considerable differences [38]. Based on this network meta-analysis, SYN was the second best graft in terms of % new bone, which was about 5.5% lower than AUT, 4.9% higher than XEN, and 8.0% higher than ALL.

XENs, and its most widely known commercial product Bio-Oss (Geistlich Pharma AG, Wolhusen, Switzerland), have been successfully used in several studies to preserve ridge dimensions following tooth extraction [34,39] and have been proven biocompatible and osteoconductive [40], as their structure and surface area promote capillary ingrowth and migration and proliferation of osteoblasts [41,42]. On the other hand, some studies have reported delayed healing regions grafted with XEN [42,43]. In the present analysis, XENs were the closely tied to the first or second best place after AUTs, with slightly lower % of

new bone (-4.9%) and slightly higher % of resorption of graft particles (+2.3%) than SYNs, which indicated acceptable biocompatibility and effectiveness.

Both osteoinductive and osteoconductive properties [44,45], as well as the preservation of bone morphogenetic proteins [46] have been attributed to ALLs used in oral surgery. However, a higher percentage of residual graft particles and less new bone formation in ALL-graft bone biopsies compared to other grafts has also been reported [47], which agrees with our results. ALL was the least effective graft than all other, which combined with the lack of osteogenic properties [48], and the risk of transmission of infectious agents, malignancies, systemic disorders (autoimmune disease), or toxins [2] render them a less appealing alternative to bone grafting. In the present analysis ALLs were the worst graft in terms of % new bone, which was 13.5% lower than AUT, 8.0% lower than SYN, and 3% lower than XEN.

4.2. Strengths and limitations

This systematic review has several strengths, including the *a priori* registration of its protocol, unrestricted literature search, attempts to maximize data output through communication with trial authors (Appendix 29), triplicate review procedures with reporting of any deviations from protocol (Appendix 30), use of individual patient data (where applicable), adjustment of effect estimates for confounders through multivariable regression, simultaneous synthesis of all available evidence by network meta-analysis, and formal assessment of our confidence in the overall quality of evidence with the GRADE approach.

However, several limitations also exist. First of all, only some of the data requests were answered from trialists, leading certain cluster-trials to be excluded due to incomplete reporting. Additionally, the reporting completeness of many identified trials was problematic, which precluded robust assessment of the risk of bias. Furthermore, the limited number of trials included in each combination of nodes makes difficult to robustly evaluate the transitivity and consistency of the network. The network could have been broken down to include all commercially-available grafts separately (Appendix 20), but this was problematic, due to the scarcity of most comparisons. Alternatively, partially-available individual patient data could have been combined with aggregate data within a Bayesian framework to increase precision [49] or a three-level hierarchical level Bayesian analysis could have been used to test across classes and subclasses of grafts simultaneously [50]. The test for inconsistency and the meta-regressions were likewise affected by this scarcity of trial and their large sampling errors due to small samples, as was seen

by their wide confidence intervals. Additionally, the use of a Bayesian framework with an informative prior could alleviate some of the high heterogeneity/imprecision of the network. Therefore, caution is warranted by the interpretation of these tests, as lack of power and the subsequent imprecision might "mask" an existing effect. Finally, for most trials the risk of bias was either unclear or high.

The findings of this review could be generalizable to most systematically healthy patients, where bone grafting is needed for a surgical procedure (sinus lift, preservation of an extraction socket or ridge augmentation) prior to implant placement. Although smokers were not excluded, this was deemed as a factor that could possibly introduce bias, due to impaired wound healing [51]. The results of this review might not be applicable to patients receiving bone grafting simultaneously with implant placement or bone grafting of periodontal defects. However, taking into account the abovementioned limitations, the generalizability of this review's findings should be viewed with caution.

4.3. Conclusions

According to mixed comparisons from randomized controlled trials of bone grafting in humans prior to implant insertion, no statistically significant differences could be found for any of the pairwise comparisons, although our confidence in these estimates is moderate to very low, mainly due to study limitations, inconsistency, and imprecision.

According to the ranking of available grafts based on the evidence network (moderate confidence):

- Autologous grafts presented the highest % of newly-formed bone, followed by synthetic grafts, xenologous grafts, and allogeneic grafts.
- Autologous grafts presented the lowest % of residual graft particles, followed by xenologous grafts, synthetic grafts, and allogeneic grafts.
- Autologous grafts presented the lowest % of connective tissue, followed by allogeneic grafts, xenologous grafts, and synthetic grafts.

4.4. Recommendations for clinical practice

Taking into account the extra burden of an additional surgery of the gold standard (autologous grafts) and the suboptimal performance of allogeneic grafts, synthetic or xenologous bone grafts can be considered as an alternative. Synthetic bone grafts are associated with increased bone formation, but

lower graft resorption compared to xenologous bone grafts. However, these recommendations should be viewed with caution, due to the limitations of the present study.

4.5. Recommendations for further research

Existing evidence is based on limited trials of small samples with unclear reporting of design characteristics. Researchers are encouraged to conduct additional adequately powered randomized trials with clear reporting based on the CONSORT statement [52]. As far as consolidation of the evidence network is concerned, trials comparing different synthetic bone substitutes with autologous or xenologous bone grafts are needed, in order to enable ranking of the separate commercially-available grafts.

Conflicts of interest

No funding existed for this study. All authors report no real or perceived conflict of interest.

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Tables

Table 1 - Direct estimates of the primary outcome. AUT = autograft; ALL = allograft; SYN = synthetic bone graft; XEN = xenograft; MD = mean difference; CI = confidence interval; UI = uncertainty interval; PrI = predictive interval.

Comparison	Studies	MD (95% CI)	I^2 (95% UI)	tau^2	95% PrI	P
AUT-ALL	2	-6.00 (-19.42,7.41)	87% (-)	82.75	-	0.380
AUT-SYN	2	-4.42 (-9.75,0.91)	68% (-)	10.09	-	0.104
AUT-XEN	2	-21.62 (-56.40,13.16)	93% (-)	587.86	-	0.223
ALL-SYN	1	25.33 (13.59,37.07)	-	0.00	-	<0.001
SYN-XEN	5	0.90 (-8.75,10.55)	94% (89%,96%)	97.78	-34.25,36.05	0.855

Table 2 - Summary of our confidence in effect estimates and ranking of treatments according to the GRADE approach.

Comparison	**Nature of the evidence**	**Confidence**	**Downgrading due to** [a]
Autograft vs allograft	Mixed	Low	Imprecision
Autograft vs synthetic graft	Mixed	Moderate	Imprecision
Autograft vs xenograft	Mixed	Very low	Study limitations; inconsistency; imprecision
Allograft vs synthetic graft	Mixed	Very low	Inconsistency; imprecision
Allograft vs xenograft	Indirect	Very low	Study limitations; imprecision
Synthetic graft vs xenograft	Mixed	Very low	Study limitations; inconsistency; imprecision
Ranking of treatments		Moderate	Study limitations

[a]See Appendix 18 for details on each judgement.

Figure Legends

Fig. 1 – PRISMA flow diagram for study identification and selection.

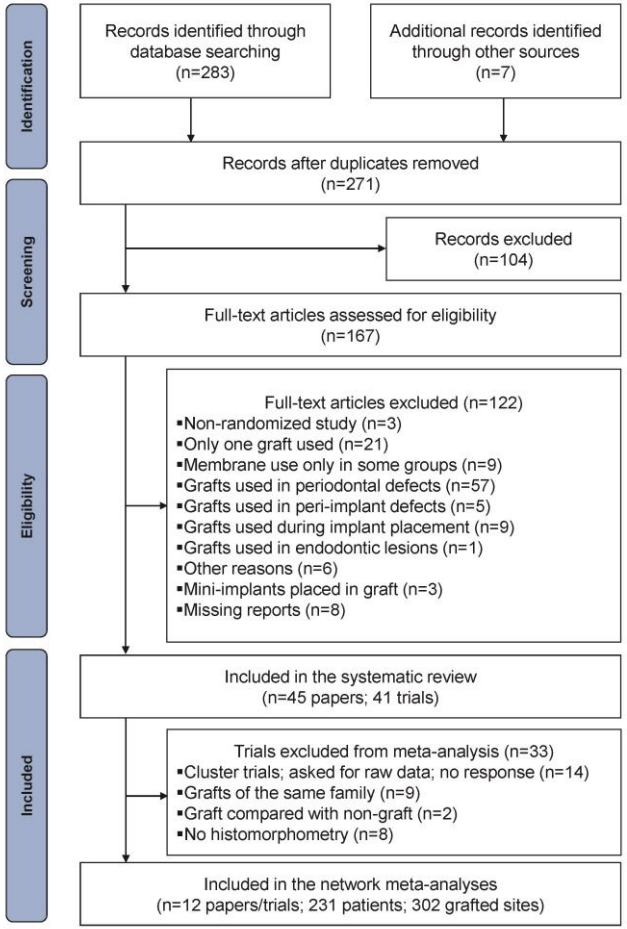

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Fig. 2 – Network diagram for the primary outcome of % new bone (12 studies; 231patients; 302 grafted sites). Joining lines indicate where head-to-head trials between interventions were identified and their risk of bias: green (low risk), yellow (moderate risk), and red (high risk). On each adjoining line is represented the number of contributing trials (number) and patients (number in parenthesis) for each comparison. Treatment nodes are proportionally sized to reflect the number of patients randomized to each intervention. AUT = autograft; ALL = allogeneic graft; SYN = synthetic bone graft; XEN = xenograft.

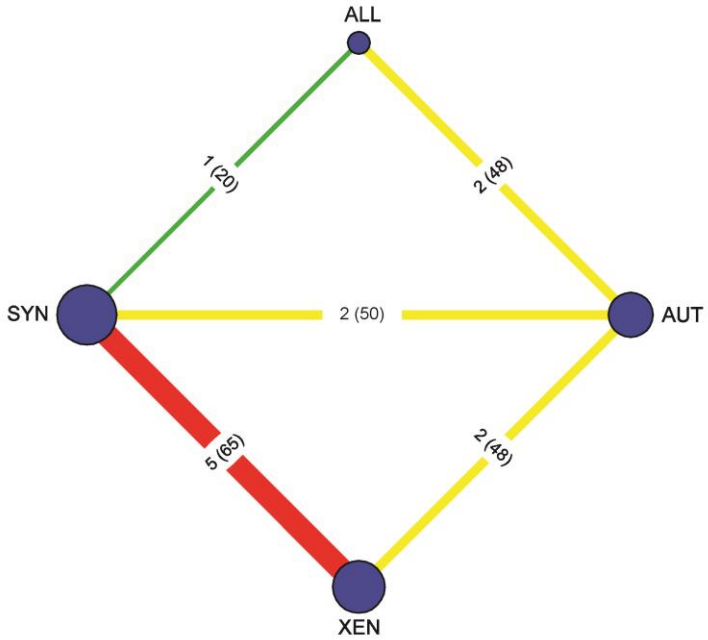

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Fig. 3 – Predictive interval plot for the primary outcome network. The black solid lines represent the confidence intervals for the summary mean difference for each comparison and the dotted red lines the respective predictive intervals (possible values in a future trial). The blue vertical line is the line of no effect (mean difference equal to 0).

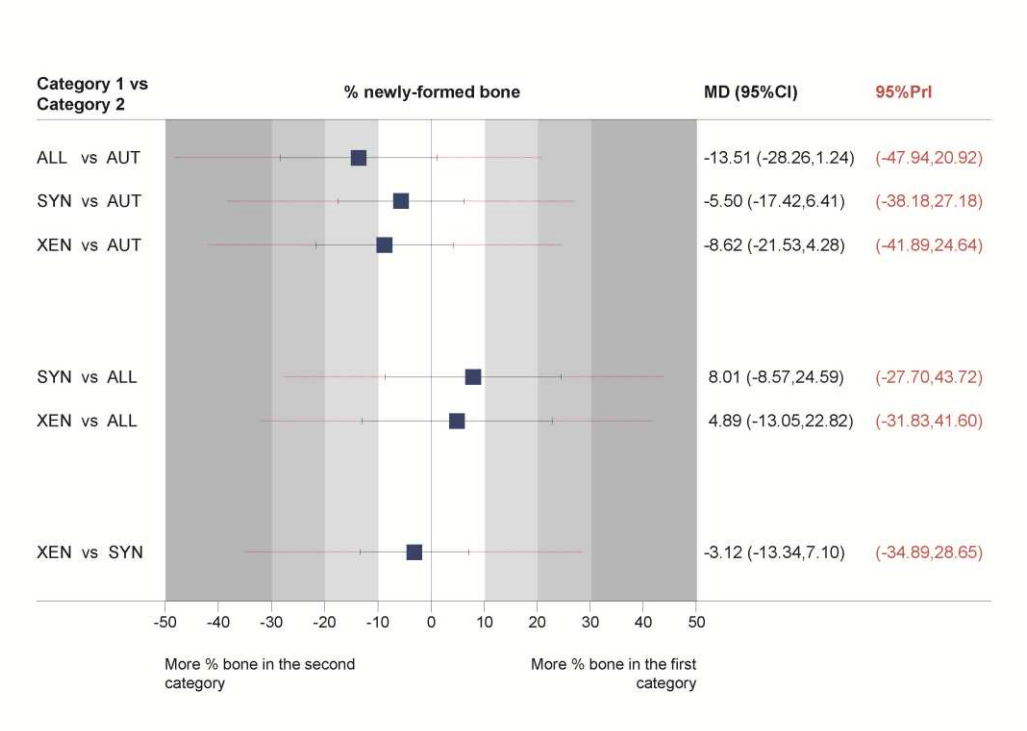

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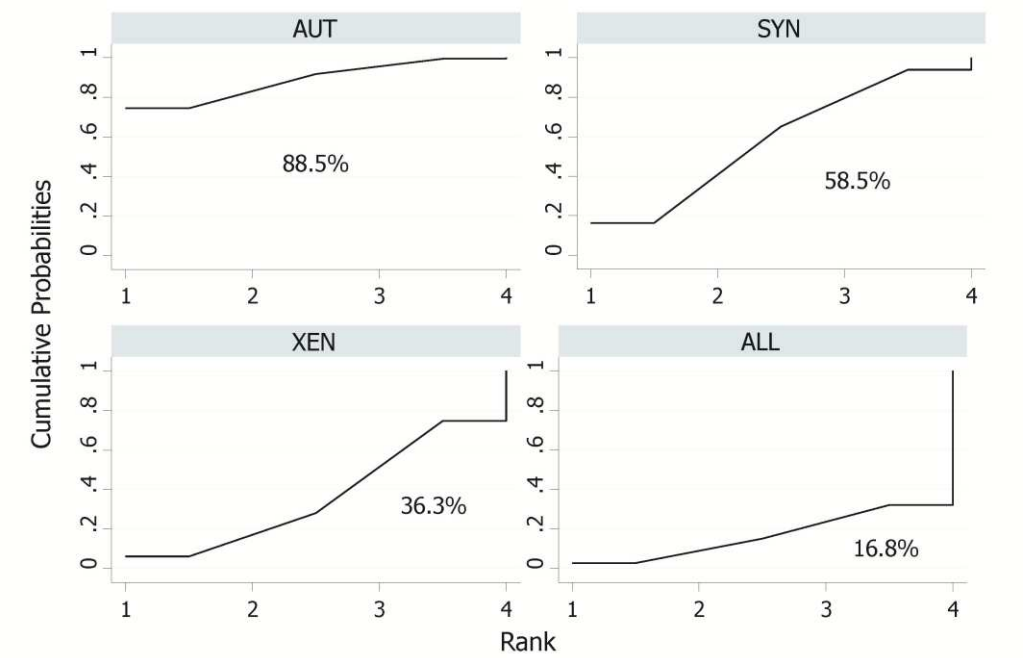
Fig. 4 – Plots of the surface under the cumulative ranking curves for all treatments in the primary outcome network. AUT = autograft; SYN = synthetic bone graft; XEN = xenograft; ALL = allograft.



Rank	AUT	ALL	SYN	XEN
Best	74.4	2.9	16.5	6.2
Mean rank	1.3	3.5	2.2	2.9
SUCRA	88.5%	16.8%	58.5%	36.3%

Comparative effectiveness of natural and synthetic bone grafts in oral and maxillofacial surgery prior to insertion of dental implants: systematic review and network meta-analysis of parallel and cluster randomized controlled trials

Appendix 1. Pre-defined inclusion and exclusion criteria according to the Participants-Intervention-Comparison-Outcomes-Study design schema and search strategy used in every electronic database together with its results (last search June 2015).

	Inclusion	**Exclusion**	
Participants	Patients of any age or sex in need of bone augmentation/preservation procedures in the oral cavity	Animal and in vitro studies.	
Intervention	▪ Any kind of bone graft or filling material used for ridge augmentation, sinus lift, socket preservation or any other bone-augmenting procedure. ▪ Combinations of grafts (almost universally of a non-autologous graft with some autologous graft) were eligible, only if the actual % contribution of each graft to the combination was reported. In this case, we classified the combination to the graft providing over 70% of the whole. ▪ In case of graft combinations with equal (i.e. 50%-70%) contributions from their components, the graft was not classified in a graft category and the trial was included in the descriptive part, but not in the quantitative one. ▪ In case a trial did not report the contribution of each graft to a graft-combination, we included this study in the descriptive part, but not in the quantitative synthesis. ▪ Membranes or other materials used to cover the surgical site will be eligible, but only if their use is consistent in all experimental groups.	▪ Studies that utilize immediate implant placement will be excluded, as all included studies will have to utilize only bone-augmenting procedures without any factor that could possibly intervene to bone healing. ▪ Studies that investigate the use of bone grafts on already inserted dental implants will also be excluded. Bone grafting for periapical endodontic lesions or periodontic tooth lesions will also be excluded, due to the risk of possibly impaired wound healing / bone formation.	
Comparison	Any kind of bone graft or filling material.	Untreated control groups will be excluded, as aim of this review is to assess the comparative effectiveness of bone grafts. The absolute effects of bone grafting have long been proved.	
Outcome - primary	The primary outcome will be the % of newly formed bone as measured through histomorphometric analyses of acquired bone samples from the augmented sites. We will include all reported time-points after the surgical procedure and we will stratify them, if possible. We anticipate that most assessments of newly-formed bone will take place during a subsequent stage of implant insertion.	-	
Outcome - secondary	▪ % of remaining graft in the sample ▪ % of immature and mature bone in the sample ▪ % of soft tissues in the sample ▪ any clinical or radiological measurement of bone status ▪ adverse effects during the healing phase or afterwards ▪ any outcome of periodontal health at the augmented or adjacent sites ▪ success and survival of dental implants inserted in the augmented bone on a secondary timepoint.	-	
Study design	Randomized controlled trials (both parallel and clustered) in any clinical setting.	Non-randomized or non-clinical studies.	
Literature search			
Database	Search	Limit	Hits
MEDLINE (through Pubmed)	(hydroxyapatite OR hydroxiapatite) AND ("bone substitute") OR ("bone graft") OR ("bone ceramic") OR ("ceramic bone") OR ("bone substitute") OR ("bone substitute healing") OR ("bone tissue engineering") OR ("artificial bone")) AND (("dental") OR ("dentistry") OR ("maxillofacial surgery") OR ("oral maxillofacial surgery") OR ("oral surgery") OR ("sinus lift"))	Randomized Controlled Trial; Humans	217
Cochrane Library (CENTRAL)	(hydroxyapatite OR hydroxiapatite) AND ("bone substitute" OR "bone graft" OR "bone ceramic" OR "ceramic bone" OR "bone substitute" OR "bone substitute healing" OR "bone tissue engineering" OR "artificial bone") AND ("dental" OR "dentistry" OR "maxillofacial surgery" OR "oral maxillofacial surgery" OR "oral surgery" OR "sinus lift")	-	47
Web of Knowledge	(hydroxyapatite OR hydroxiapatite) AND ("bone substitute" OR "bone graft" OR "bone ceramic" OR "ceramic bone" OR "bone substitute" OR "bone substitute healing" OR "bone tissue engineering" OR "artificial bone") AND ("dental" OR "dentistry" OR "maxillofacial surgery" OR "oral maxillofacial surgery" OR "oral surgery" OR "sinus lift") AND random*	Dentistry oral surgery medicine	18
Virtual Health Library	(hydroxyapatite OR hydroxiapatite) AND ("bone substitute" OR "bone graft" OR "bone ceramic" OR "ceramic bone" OR "bone substitute" OR "bone substitute healing" OR "bone tissue engineering" OR "artificial bone") AND ("dental" OR "dentistry" OR "maxillofacial surgery" OR "oral maxillofacial surgery" OR "oral surgery" OR "sinus lift") AND random*	Limit to humans; exclude MEDLINE+CENTRAL	1

Appendix 2. Details of data synthesis and assessments of heterogeneity.

Heterogeneity in pairwise analyses was assessed with the I^2 metric, defined as the proportion of total variability in the results explained by heterogeneity, and not chance (Higgins and Thompson 2002). The 95% uncertainty intervals (95% UI) (similar to CIs) around the I^2 were calculated (Ioannidis et al. 2007) using the non-central χ^2 approximation of Q. For network meta-analysis, a common heterogeneity variable for all comparisons (tau) was assumed, which is the estimated standard deviation of underlying effects of treatment across studies in a meta-analysis (Salanti, 2012).

The absolute and relative presence of heterogeneity within pairwise meta-analyses was calcuated with the tau^2 metric and I^2 statistic, respectively. I^2 thresholds were considered to represent heterogeneity that might not be important (0% to 40%), might be moderate heterogeneity (30% to 60%), might be substantial heterogeneity (50% to 90%), and might be considerable heterogeneity (75% to 100%), considering also the magnitude and direction of treatment effects and strength of evidence for heterogeneity.

The assumption of transitivity within the network was assessed by exploring the distribution of patient characteristics, similarity of interventions, and study design across comparisons. Based on the specific inclusion/exclusion criteria set, only adult patients (since insertion of dental implants is contra-indicated in growing patients), with similar level of oral hygiene (having experienced tooth loss – i.e. in need of dental implants), and with similar medical history (compatible with the surgical insertion of implants) were included. Therefore, as all only randomized trials with general patient inclusion criteria were included in this systematic review, small deviations to patient characteristics are more likely to be due to chance, rather than real clinical inhomogeneity.

Evidence for consistency in the network was assessed in two ways. First, a loop-specific approach was used to investigate consistency within every closed triangular or quadratic loop in every network as the difference between direct and indirect estimates for a specific treatment comparison (inconsistency factor) in the loop (Salanti et al., 2009). Inconsistent loops were identified as those yielding a 95% CI excluding zero. Second, the network-wide method of node-splitting was employed on a frequentist framework (Dias et al., 2010) to separates evidence on a particular comparison into "direct" and "indirect", by excluding one direct comparison at a time and estimating the indirect treatment effect for the excluded comparison (*network sidesplit* macro in Stata). Finally, the design-by-treatment interaction

model was used that provides a single inference, using a χ^2 test, about the plausibility of assuming consistency throughout the entire network and the model fit was compared to the original analysis (Higgins et al., 2012).

On a patient level, we made use of available raw data and fitted multivariable regression models to calculate the impact of any effect modifiers on the primary outcome. We then pooled the impact from each study across all studies to estimate its overall impact with random-effects meta-analyses. On a study level, we performed network meta-regression to explore sources of heterogeneity and/or inconsistency. When potential evidence of heterogeneity was identified, we first checked for any mistakes and inconsistencies in data extraction and entry. We then evaluated if the network meta-regression model fit was substantial altered compared to the original (by reestimating the models by maximum likelihood and performing a likelihood ratio test) and if so, treatments were re-ranked.

Appendix 3. List of excluded and included studies.

Nr.	Paper	Status
	Excluded reports	
1	AboElsaad NS, Soory M, Gadalla LM, Ragab LI, Dunne S, Zalata KR, et al. Effect of soft laser and bioactive glass on bone regeneration in the treatment of infra-bony defects (a clinical study). Lasers in medical science. 2009;24(3):387-95.	Excluded by title/abstract
2	Abrahamsson P, Walivaara DA, Isaksson S, Andersson G. Periosteal expansion before local bone reconstruction using a new technique for measuring soft tissue profile stability: a clinical study. Journal of oral and maxillofacial surgery. 2012;70(10):e521-30.	Excluded by title/abstract
3	Agarwal A, Gupta ND. Comparative evaluation of decalcified freeze-dried bone allograft use alone and in combination with polylactic acid, polyglycolic acid membrane in the treatment of noncontained human periodontal infrabony defects. Quintessence international (Berlin, Germany : 1985). 2012;43(9):761-8. Epub 2012/10/09.	Excluded by title/abstract
4	Aimetti M, Pigella E, Romano F, Debernardi C. Treatment of mandibular class II furcation defects by the use of amelogenins and autologous bone. Two case reports. Minerva stomatologica. 2005;54(10):583-91. Epub 2005/10/15.	Excluded by title/abstract
5	Alonso N, Tanikawa DY, Freitas Rda S, Canan L, Jr., Ozawa TO, Rocha DL. Evaluation of maxillary alveolar reconstruction using a resorbable collagen sponge with recombinant human bone morphogenetic protein-2 in cleft lip and palate patients. Tissue engineering Part C, Methods. 2010;16(5):1183-9. Epub 2010/02/19.	Excluded by title/abstract
6	Annen BM, Ramel CF, Hammerle CH, Jung RE. Use of a new cross-linked collagen membrane for the treatment of peri-implant dehiscence defects: a randomised controlled double-blinded clinical trial. European journal of oral implantology. 2011;4(2):87-100. Epub 2011/08/03.	Excluded by title/abstract
7	Antoun H, Sitbon JM, Martinez H, Missika P. A prospective randomized study comparing two techniques of bone augmentation: onlay graft alone or associated with a membrane. Clinical oral implants research. 2001;12(6):632-9. Epub 2001/12/12.	Excluded by title/abstract
8	Barone A, Orlando B, Cingano L, Marconcini S, Derchi G, Covani U. A randomized clinical trial to evaluate and compare implants placed in augmented versus non-augmented extraction sockets: 3-year results. Journal of periodontology. 2012;83(7):836-46. Epub 2011/12/07.	Excluded by title/abstract
9	Becker J, Al-Nawas B, Klein MO, Schliephake H, Terheyden H, Schwarz F. Use of a new cross-linked collagen membrane for the treatment of dehiscence-type defects at titanium implants: a prospective, randomized-controlled double-blinded clinical multicenter study. Clinical oral implants research. 2009;20(7):742-9. Epub 2009/03/24.	Excluded by title/abstract
10	Bettega G, Cinquin P, Lebeau J, Raphael B. Computer-assisted orthognathic surgery: clinical evaluation of a mandibular condyle repositioning system. Journal of oral and maxillofacial surgery. 2002;60(1):27-34; discussion -5. Epub 2002/01/05.	Excluded by title/abstract
11	Blaszczyszyn A, Kubasiewicz-Ross P, Gedrange T, Dominiak M. Influence of semipermanent cement application used in immediately loaded, implant-supported restorations on crestal bone resorption. Annales Academiae Medicae Stetinensis. 2013;59(1):66-75. Epub 2013/01/01.	Excluded by title/abstract
12	Boëck-Neto RJ, Gabrielli M, Lia R, Marcantonio E, Shibli JA. Histomorphometrical analysis of bone formed after maxillary sinus floor augmentation by grafting with a combination of autogenous bone and demineralized freeze-dried bone allograft or hydroxyapatite. Journal of periodontology [Internet]. 2002; (3):[266-70 pp.].	Excluded by title/abstract
13	Borges FL, Dias RO, Piattelli A, Onuma T, Gouveia Cardoso LA, Salomao M, et al. Simultaneous sinus membrane elevation and dental implant placement without bone graft: a 6-month follow-up study. Journal of periodontology. 2011;82(3):403-12. Epub 2010/11/09.	Excluded by title/abstract
14	Brkovic BM, Prasad HS, Rohrer MD, Konandreas G, Agrogiannis G, Antunovic D, et al. Beta-tricalcium phosphate/type I collagen cones with or without a barrier membrane in human extraction socket healing: clinical, histologic, histomorphometric, and immunohistochemical evaluation. Clinical oral investigations. 2012;16(2):581-90. Epub 2011/03/04.	Excluded by title/abstract
15	Burger EA, Meshkini H, Lindeboom JA. One versus two titanium screw fixation of autologous onlay bone grafts in the anterior maxilla: a randomised histological pilot study. European journal of oral implantology. 2011;4(3):219-25. Epub 2011/11/02.	Excluded by title/abstract
16	Butz F, Bachle M, Ofer M, Marquardt K, Kohal RJ. Sinus augmentation with bovine hydroxyapatite/synthetic peptide in a sodium hyaluronate carrier (PepGen P-15 Putty): a clinical investigation of different healing times. International journal of oral & maxillofacial implants [Internet]. 2011; (6):[1317-23 pp.].	Excluded by title/abstract
17	Calongne KB, Aichelmann-Reidy ME, Yukna RA, Mayer ET. Clinical comparison of microporous biocompatible composite of PMMA, PHEMA and calcium hydroxide grafts and expanded polytetrafluoroethylene barrier membranes in human mandibular molar Class II furcations. A case series. Journal of periodontology. 2001;72(10):1451-9. Epub 2001/11/09.	Excluded by title/abstract
18	Canullo L, Dellavia C. Sinus lift using a nanocrystalline hydroxyapatite silica gel in severely resorbed maxillae: histological preliminary study. Clinical implant dentistry and related research. 2009;11 Suppl 1:e7-13. Epub 2009/02/18.	Excluded by title/abstract
19	Chen CC, Wang HL, Smith F, Glickman GN, Shyr Y, O'Neal RB. Evaluation of a collagen membrane with and without bone grafts in treating periodontal intrabony defects. Journal of periodontology. 1995;66(10):838-47. Epub 1995/10/01.	Excluded by title/abstract

20	Choi BH, Yoo JH, Sung KJ. Radiographic comparison of osseous healing after maxillary sinusotomy performed with and without a periosteal pedicle. Oral surgery, oral medicine, oral pathology, oral radiology, and endodontics. 1996;82(4):375-8. Epub 1996/10/01.	Excluded by title/abstract
21	Choi KS, Kan JY, Boyne PJ, Goodacre CJ, Lozada JL, Rungcharassaeng K. The effects of resorbable membrane on human maxillary sinus graft: a pilot study. The International journal of oral & maxillofacial implants. 2009;24(1):73-80. Epub 2009/04/07.	Excluded by title/abstract
22	Cordaro L, Bosshardt DD, Palattella P, Rao W, Serino G, Chiapasco M. Maxillary sinus grafting with Bio-Oss (R) or Straumann (R) Bone Ceramic: histomorphometric results from a randomized controlled multicenter clinical trial. Clinical oral implants research. 2008;19(8):796-803.	Excluded by title/abstract
23	Cornelini R, Cangini F, Martuscelli G, Wennstrom J. Deproteinized bovine bone and biodegradable barrier membranes to support healing following immediate placement of transmucosal implants: a short-term controlled clinical trial. Int J Periodont Restor Dent. 2004;24(6):555-63.	Excluded by title/abstract
24	Crespi R, Cappare P, Addis A, Gherlone E. Injectable Magnesium-Enriched Hydroxyapatite Putty in Peri-Implant Defects: A Histomorphometric Analysis in Pigs. International journal of oral & maxillofacial implants. 2012;27(1):95-101.	Excluded by title/abstract
25	Dahlin C, Simion M, Hatano N. Long-term follow-up on soft and hard tissue levels following guided bone regeneration treatment in combination with a xenogeneic filling material: a 5-year prospective clinical study. Clinical implant dentistry and related research [Internet]. 2010; (4):[263-70 pp.].	Excluded by title/abstract
26	Del Fabbro M, Testori T, Francetti L, Weinstein D. Systematic review of survival rates for implants placed in the grafted maxillary sinus. International journal of periodontics & restorative dentistry. 2004;24(6):565-+.	Excluded by title/abstract
27	Engler-Hamm D, Cheung WS, Yen A, Stark PC, Griffin T. Ridge Preservation Using a Composite Bone Graft and a Bioabsorbable Membrane With and Without Primary Wound Closure: A Comparative Clinical Trial. Journal of periodontology. 2011;82(3):377-87.	Excluded by title/abstract
28	Felice P, Cannizzaro G, Checchi V, Marchetti C, Pellegrino G, Censi P, et al. Vertical bone augmentation versus 7-mm-long implants in posterior atrophic mandibles. Results of a randomised controlled clinical trial of up to 4 months after loading. European journal of oral implantology. 2009;2(1):7-20. Epub 2010/05/15.	Excluded by title/abstract
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214	Cardaropoli D, Tamagnone L, Roffredo A, Gaveglio L, Cardaropoli G. Socket preservation using bovine bone mineral and collagen membrane: a randomized controlled clinical trial with histologic analysis. Int J Periodont Restor Dent. 2012;32(4):421-30.	Excluded; report unobtained
215	Kao DW, Kubota A, Nevins M, Fiorellini JP. The negative effect of combining rhBMP-2 and Bio-Oss on bone formation for maxillary sinus augmentation. Int J Periodont Restor Dent. 2012;32(1):61-7. Epub 2012/01/19.	Excluded; report unobtained
216	Kutkut A, Andreana S, Monaco E, Jr. Clinical and radiographic evaluation of single-tooth dental implants placed in grafted extraction sites: a one-year report. Journal of the International Academy of Periodontology. 2013;15(4):113-24. Epub 2013/12/25.	Excluded; report unobtained
217	Merli M, Moscatelli M, Mariotti G, Rotundo R, Nieri M. Autogenous bone versus deproteinised bovine bone matrix in 1-stage lateral sinus floor elevation in the severely atrophied maxilla: a randomised controlled trial. Eur J Oral Implantol 2013;6:27–37.	Excluded; report unobtained
218	Nevins ML, Camelo M, Schupbach P, Nevins M, Kim SW, Kim DM. Human buccal plate extraction socket regeneration with recombinant human platelet-derived growth factor BB or enamel matrix derivative. Int J Periodont Restor Dent. 2011;31(5):481-92. Epub 2011/08/17.	Excluded; report unobtained
219	Oghli AA, Steveling H. Ridge preservation following tooth extraction: a comparison between atraumatic extraction and socket seal surgery. Quintessence international (Berlin, Germany : 1985). 2010;41(7):605-9. Epub 2010/07/09.	Excluded; report unobtained
220	Rebaudi A, Silvestrini P, Trisi P. Use of a resorbable hydroxyapatite-collagen chondroitin sulfate material on immediate postextraction sites: a clinical and histologic study. Int J Periodont Restor Dent. 2003;23(4):371-9. Epub 2003/09/06.	Excluded; report unobtained
221	Lindgren C, Mordenfeld A, Hallman M. A prospective 1-year clinical and radiographic study of implants placed after maxillary sinus floor augmentation with synthetic biphasic calcium phosphate or deproteinized bovine bone. Clinical implant dentistry and related research. 2012;14(1):41-50. Epub 2010/05/25.	Excluded; mini-implants placed in graft
222	Lindgren C, Mordenfeld A, Johansson CB, Hallman M. A 3-year clinical follow-up of implants placed in two different biomaterials used for sinus augmentation. The International journal of oral & maxillofacial implants. 2012;27(5):1151-62. Epub 2012/10/12.	Excluded; mini-implants placed in graft
223	Lindgren C, Sennerby L, Mordenfeld A, Hallman M. Clinical histology of microimplants placed in two different biomaterials. The International journal of oral & maxillofacial implants. 2009;24(6):1093-100. Epub 2010/02/18.	Excluded; mini-implants placed in graft
224	Poulias E, Greenwell H, Hill M, Morton D, Vidal R, Shumway B, Peterson TL. Ridge preservation comparing socket allograft alone to socket allograft plus facial overlay xenograft: a clinical and histologic study in humans. J Periodontol. 2013 Nov;84(11):1567-75.	Excluded; trial arms different both for graft and surgical technique
225	Poulias E. Ridge preservation comparing the clinical and histologic healing of an intrasocket allograft vs. a facial overlay xenograft using a bioresorbable barrier membrane. University of Louisville 2012; Masters Thesis.	Excluded; trial arms different both for graft and surgical technique
226	Bertoldi C, Zaffe D, Consolo U. Polylactide/polyglycolide copolymer in bone defect healing in humans. Biomaterials. 2008;29(12):1817-23. Epub 2008/02/01.	Excluded; graft used in periapical cysts
Included reports		
227	Bettega G, Brun JP, Boutonnat J, Cracowski JL, Quesada JL, Hegelhofer H, et al. Autologous platelet concentrates for bone graft enhancement in sinus lift procedure. Transfusion. 2009;49(4):779-85. Epub 2009/01/28.	Included in SR; excluded from NMA: cluster trial no raw data; requested through e-mail.
228	Calasans-Maia M, Resende R, Fernandes G, Calasans-Maia J, Alves AT, Granjeiro JM. A randomized controlled clinical trial to evaluate a new xenograft for alveolar socket preservation. Clin Oral Implants Res. 2014 Oct;25(10):1125-30.	Included maually in SR; excluded from NMA: compared grafts from the same graft family.

229	Checchi V, Savarino L, Montevecchi M, Felice P, Checchi L. Clinical-radiographic and histological evaluation of two hydroxyapatites in human extraction sockets: a pilot study. Int J Oral Maxillofac Surg. 2011;40(5):526-32. Epub 2011/02/02.	Included in SR; excluded from NMA: compared grafts from the same graft family.
230	Cordaro L, Bosshardt DD, Palattella P, Rao W, Serino G, Chiapasco M. Maxillary sinus grafting with Bio-Oss or Straumann Bone Ceramic: histomorphometric results from a randomized controlled multicenter clinical trial. Clinical oral implants research. 2008;19(8):796-803.	Included in SR; excluded from NMA: cluster trial no raw data; requested through e-mail.
231	Cordaro L, Torsello F, Morcavallo S, di Torresanto VM. Effect of bovine bone and collagen membranes on healing of mandibular bone blocks: a prospective randomized controlled study. Clinical oral implants research. 2011;22(10):1145-50. Epub 2011/02/12.	Included in SR; excluded from NMA: compared grafts from the same graft family.
232	Corinaldesi G, Piersanti L, Piattelli A, Iezzi G, Pieri F, Marchetti C. Augmentation of the floor of the maxillary sinus with recombinant human bone morphogenetic protein-7: a pilot radiological and histological study in humans. The British journal of oral & maxillofacial surgery. 2013;51(3):247-52.	Included in SR; excluded from NMA: cluster trial no raw data; requested through e-mail.
233	Crespi R, Cappare P, Gherlone E. Comparison of magnesium-enriched hydroxyapatite and porcine bone in human extraction socket healing: a histologic and histomorphometric evaluation. The International journal of oral & maxillofacial implants. 2011;26(5):1057-62. Epub 2011/10/20.	Included in SR; excluded from NMA: cluster trial no raw data; requested through e-mail.
234	Crespi R, Cappare P, Gherlone E. Magnesium-enriched hydroxyapatite compared to calcium sulfate in the healing of human extraction sockets: radiographic and histomorphometric evaluation at 3 months. Journal of periodontology. 2009;80(2):210-8. Epub 2009/02/04.	Included in SR; excluded from NMA: cluster trial no raw data; requested through e-mail.
235	Crespi R, Mariani E, Benasciutti E, Cappare P, Cenci S, Gherlone E. Magnesium-enriched hydroxyapatite versus autologous bone in maxillary sinus grafting: combining histomorphometry with osteoblast gene expression profiles ex vivo. Journal of periodontology. 2009;80(4):586-93.	Included in SR; excluded from NMA: cluster trial no raw data; requested through e-mail.
236	de Freitas RM, Susin C, Spin-Neto R, Marcantonio C, Wikesjo UM, Pereira LA, et al. Horizontal ridge augmentation of the atrophic anterior maxilla using rhBMP-2/ACS or autogenous bone grafts: a proof-of-concept randomized clinical trial. Journal of clinical periodontology. 2013;40(10):968-75. Epub 2013/09/04.	Included in SR; excluded from NMA: graft compared to growth factor.
237	Felice P, Marchetti C, Piattelli A, Pellegrino G, Checchi V, Worthington H, et al. Vertical ridge augmentation of the atrophic posterior mandible with interpositional block grafts: bone from the iliac crest versus bovine anorganic bone. Eur J Oral Implantology. 2008;1(3):183-98.	Included in SR; excluded from NMA: cluster trial no raw data; requested through e-mail.
238	Froum S, Cho SC, Elian N, Rosenberg E, Rohrer M, Tarnow D. Extraction sockets and implantation of hydroxyapatites with membrane barriers: a histologic study. Implant dentistry. 2004;13(2):153-64. Epub 2004/06/05.	Included in NMA
239	Froum S, Cho SC, Rosenberg E, Rohrer M, Tarnow D. Histological comparison of healing extraction sockets implanted with bioactive glass or demineralized freeze-dried bone allograft: a pilot study. Journal of periodontology. 2002;73(1):94-102. Epub 2002/02/16.	Included in NMA
240	Froum SJ, Wallace SS, Cho SC, Elian N, Tarnow DP. Histomorphometric comparison of a biphasic bone ceramic to anorganic bovine bone for sinus augmentation: 6- to 8-month postsurgical assessment of vital bone formation. A pilot study. Int J Periodont Restor Dent. 2008;28:273-81.	Included in NMA
241	Galindo-Moreno P, Moreno-Riestra I, Avila G, Padial-Molina M, Paya JA, Wang HL, et al. Effect of anorganic bovine bone to autogenous cortical bone ratio upon bone remodeling patterns following maxillary sinus augmentation. Clinical oral implants research. 2011;22(8):857-64.	Included in SR; excluded from NMA: compared grafts from the same graft family.
242	Garlini G, Redemagni M, Canciani E, Dellavia C. Maxillary sinus fl oor augmentation with vegetal hydroxyapatite "versus" demineralized bovine bone: A randomized clinical study with a split-mouth design. J Dent Implant 2014;4:118-25.	Included manually in NMA
243	Gholami GA, Najafi B, Mashhadiabbas F, Goetz W, Najafi S. Clinical, histologic and histomorphometric evaluation of socket preservation using a synthetic nanocrystalline hydroxyapatite in comparison with a bovine xenograft: a randomized clinical trial. Clin Oral Implants Res. 2012 Oct;23(10):1198-204.	Included manually in SR; excluded from NMA: compared grafts from the same graft family.
244	Hermund NU, Stavropoulos A, Donatsky O, Nielsen H, Clausen C, Reibel J, et al. Reimplantation of cultivated human bone cells from the posterior maxilla for sinus floor augmentation. Histological results from a randomized controlled clinical trial. Clinical oral implants research. 2012;23(9):1031-7. Epub 2011/11/19.	Included in SR; excluded from NMA: compared grafts from the same graft family.
245	Jun SH, Ahn JS, Lee JI, Ahn KJ, Yun PY, Kim YK. A prospective study on the effectiveness of newly developed autogenous tooth bone graft material for sinus bone graft procedure. J Adv Prosthodont. 2014 Dec;6(6):528-38.	Included manually in NMA
246	Koch FP, Becker J, Terheyden H, Capsius B, Wagner W. A prospective, randomized pilot study on the safety and efficacy of recombinant human growth and differentiation factor-5 coated onto β-tricalcium phosphate for sinus lift augmentation. Clin Oral Implants Res 2010;21:1301-8.	Included in SR; excluded from NMA: compared grafts from the same graft family.
247	Kotsakis GA, Salama M, Chrepa V, Hinrichs JE, Gaillard P. A randomized, blinded, controlled clinical study of particulate anorganic bovine bone mineral and calcium phosphosilicate putty bone substitutes for socket preservation. The International journal of oral & maxillofacial implants. 2014;29(1):141-51. Epub 2014/01/24.	Included in SR; excluded from NMA: no histomorphometry.
248	Kuhl S, Brochhausen C, Gotz H, Filippi A, Payer M, d'Hoedt B, et al. The influence of bone substitute materials on the bone volume after maxillary sinus augmentation: a microcomputerized tomography study. Clinical oral investigations. 2013;17(2):543-51. Epub 2012/04/28.	Included in SR; excluded from NMA: no histomorphometry.
249	Kuhl S, Gotz H, Brochhausen C, Jakse N, Filippi A, d'Hoedt B, et al. The influence of substitute materials on bone density after maxillary sinus augmentation: a microcomputed tomography study. The International journal of oral & maxillofacial implants. 2012;27(6):1541-6.	Included in SR; excluded from NMA: no histomorphometry.

250	Kurkcu M, Benlidayi ME, Cam B, Sertdemir Y. Anorganic bovine-derived hydroxyapatite vs ?-tricalcium phosphate in sinus augmentation: a comparative histomorphometric study. Journal of oral implantology [Internet]. 2012:[519-26 pp.].	Included in NMA
251	Lee CY, Rohrer MD, Prasad HS. Immediate loading of the grafted maxillary sinus using platelet rich plasma and autogenous bone: a preliminary study with histologic and histomorphometric analysis. Implant dentistry. 2008;17(1):59-73. Epub 2008/03/12.	Included in SR; excluded from NMA: cluster trial no raw data adequately reported (patient clustering); requested through e-mail.
252	Mardas N, Chadha V, Donos N. Alveolar ridge preservation with guided bone regeneration and a synthetic bone substitute or a bovine-derived xenograft: a randomized, controlled clinical trial. Clinical oral implants research. 2010;21(7):688-98. Epub 2010/07/20.	Included in SR; excluded from NMA: no histomorphometry.
253	Mardas N, D'Aiuto F, Mezzomo L, Arzoumanidi M, Donos N. Radiographic alveolar bone changes following ridge preservation with two different biomaterials. Clinical oral implants research. 2011;22(4):416-23. Epub 2011/05/13.	Included in SR; excluded from NMA: no histomorphometry.
254	Meijndert L, Raghoebar GM, Meijer HJA, Vissink A. Clinical and radiographic characteristics of single-tooth replacements preceded by local ridge augmentation: a prospective randomized clinical trial. Clin Oral Implants Res 2008;19:1295–1303.	Included in SR; excluded from NMA: no histomorphometry.
255	Meijndert L, Raghoebar GM, Schupbach P, Meijer HJ, Vissink A. Bone quality at the implant site after reconstruction of a local defect of the maxillary anterior ridge with chin bone or deproteinised cancellous bovine bone. Int J Oral Maxillofac Surg. 2005;34(8):877-84.	Included in NMA
256	Molly L, Vandromme H, Quirynen M, Schepers E, Adams JL, van Steenberghe D. Bone formation following implantation of bone biomaterials into extraction sites. Journal of periodontology. 2008;79(6):1108-15. Epub 2008/06/07.	Included in SR; excluded from NMA: cluster trial no raw data; requested through e-mail.
257	Mordenfeld A, Johansson CB, Albrektsson T, Hallman M. A randomized and controlled clinical trial of two different compositions of deproteinized bovine bone and autogenous bone used for lateral ridge augmentation. Clinical oral implants research. 2014;25(3):310-20. Epub 2013/04/05.	Included in SR; excluded from NMA: cluster trial no raw data; requested through e-mail.
258	Patel K, Mardas N, Donos N. Radiographic and clinical outcomes of implants placed in ridge preserved sites: a 12-month post-loading follow-up. Clinical oral implants research. 2013;24(6):599-605. Epub 2012/06/08.	Included in SR; excluded from NMA: no histomorphometry.
259	Piattelli A, Degidi M, Di Stefano DA, Rubini C, Fioroni M, Strocchi R. Microvessel density in alveolar ridge regeneration with autologous and alloplastic bone. Implant dentistry. 2002;11(4):370-5. Epub 2003/01/10.	Included in SR; excluded from NMA: no histomorphometry.
260	Pikdoken L, Gurbuzer B, Kucukodaci Z, Urban M, Baris E, Tezulas E. Scintigraphic, Histologic, and Histomorphometric Analyses of Bovine Bone Mineral and Autogenous Bone Mixture in Sinus Floor Augmentation: A Randomized Controlled Trial-Results After 4 Months of Healing. Journal of Oral and Maxillofacial Surgery. 2011;69(1):160-9.	Included in SR; excluded from NMA: compared grafts from the same graft family.
261	Raghoebar GM, Schortinghuis J, Liem RS, Ruben JL, van der Wal JE, Vissink A. Does platelet-rich plasma promote remodeling of autologous bone grafts used for augmentation of the maxillary sinus floor? Clinical oral implants research. 2005;16(3):349-56. Epub 2005/05/10.	Included in SR; excluded from NMA: cluster trial no raw data; requested through e-mail.
262	Rickert D, Sauerbier S, Nagursky H, Menne D, Vissink A, Raghoebar GM. Maxillary sinus floor elevation with bovine bone mineral combined with either autogenous bone or autogenous stem cells: a prospective randomized clinical trial. Clinical oral implants research. 2011;22(3):251-8.	Included in SR; excluded from NMA: graft compared to graft with stem cells.
263	Schmitt CM, Doering H, Schmidt T, Lutz R, Neukam FW, Schlegel KA. Histological results after maxillary sinus augmentation with Straumann(R) BoneCeramic, Bio-Oss(R), Puros(R), and autologous bone. A randomized controlled clinical trial. Clin Oral Imp Res 2013;24(5):576-85.	Included in SR; excluded from NMA: cluster trial no raw data; requested through e-mail.
264	Shirmohammadi A, Roshangar L, Chitsazi MT, Pourabbas R, Faramarzie M, Rahmanpour N. Comparative Study on the Efficacy of Anorganic Bovine Bone (Bio-Oss) and Nanocrystalline Hydroxyapatite (Ostim) in Maxillary Sinus Floor Augmentation. International Scholarly Research Notices 2014; 967091.	Included in NMA
265	Stavropoulos A, Becker J, Capsius B, Acil Y, Wagner W, Terheyden H. Histological evaluation of maxillary sinus floor augmentation with recombinant human growth and differentiation factor-5-coated beta-tricalcium phosphate: results of a multicenter randomized clinical trial. Journal of clinical periodontology. 2011;38(10):966-74. Epub 2011/07/30.	Included in SR; excluded from NMA: compared grafts from the same graft family.
267	Szabo G, Huys L, Coulthard P, Maiorana C, Garagiola U, Barabas J, et al. A prospective multicenter randomized clinical trial of autogenous bone versus beta-tricalcium phosphate graft alone for bilateral sinus elevation: histologic and histomorphometric evaluation. The International journal of oral & maxillofacial implants. 2005;20(3):371-81. Epub 2005/06/25.	Included in NMA
268	Tosta M, Cortes AR, Correa L, Pinto Ddos S, Jr., Tumenas I, Katchburian E. Histologic and histomorphometric evaluation of a synthetic bone substitute for maxillary sinus grafting in humans. Clinical oral implants research. 2013;24(8):866-70. Epub 2011/12/16.	Included in NMA
269	Wagner W, Wiltfang J, Pistner H, Yildirim M, Ploder B, Chapman M, et al. Bone formation with a biphasic calcium phosphate combined with fibrin sealant in maxillary sinus floor elevation for delayed dental implant. Clinical oral implants research. 2012;23(9):1112-7. Epub 2012/08/16.	Included in SR; excluded from NMA: cluster trial no raw data; requested through e-mail.
270	Wiltfang J, Schlegel KA, Schultze-Mosgau S, Nkenke E, Zimmermann R, Kessler P. Sinus floor augmentation with beta-tricalciumphosphate (beta-TCP): does platelet-rich plasma promote its osseous integration and degradation? Clinical oral implants research. 2003;14(2):213-8.	Included in SR; excluded from NMA: cluster trial no raw data; requested through e-mail.
271	Wood RA, Mealey BL. Histologic comparison of healing after tooth extraction with ridge preservation using mineralized versus demineralized freeze-dried bone allograft. Journal of periodontology. 2012;83(3):329-36. Epub 2011/07/14.	Included in NMA

272	Xavier SP, Dias RR, Sehn FP, Kahn A, Chaushu L, Chaushu G. Maxillary sinus grafting with autograft vs. fresh frozen allograft: a split-mouth histomorphometric study. Clin. Oral Impl. Res. 00, 2014, 1–6.	Included manually in NMA

SR, systematic review; BMA, meta-analysis.

Appendix 4. Demographics of the 41 trials included in this systematic review.

Nr	Study	Multi center	Setting	Raw data	Country	Patients (M/F)	Age (yrs)
	Cluster trials						
1	Bettega 2009	No	Clinic	No	France	18 (5/13)	50.5
2	Cordaro 2008	Yes	University/practice	No	Italy	37 (NR)	NR
3	Corinaldesi 2013	No	University	No	Italy	9 (3/6)	50.0
4	Crespi 2009a$	No	University	No	Italy	15 (8/7)	51.3
5	Crespi 2009b	No	University	No	Italy	15 (9/6)	54.2
6	Crespi 2011$	No	University	No	Italy	15 (7/8)	53.7
7	Felice 2008	No	University	No	Italy	10 (4/6)	54.0
8	Froum 2002$	No	University	Yes	USA	19 (12/7)	NR
9	Froum 2004$	No	University	Yes	USA	15 (9/6)	48.1
10	Froum 2008	No	University	Yes	USA	12 (NR)	NR
11	Garlini 2014	No	University	Yes	Italy	5 (2/3)	57.0
12	Gholami 2012	No	NR	No	Iran	12 (4/8)	44.6
13	Kotsakis 2014$	No	University	No	USA	18 (12/6)	41.6
14	Lee 2008	No	Practice	Yes	USA	41 (14/27)	59.0
15	Molly 2008$	No	University	No	Belgium	8 (1/7)	53.0
16	Mordenfeld 2014	No	University	No	Sweden	13 (6/7)	59.6
17	Raghoebar 2005	No	University	No	Netherlands	5 (2/3)	58.4
18	Rickert 2011	No	University	Yes	Netherlands	12 (NR)	60.8
19	Schmitt 2013	No	University	No	Germany	30 (13/17)	NR
20	Shirmohammadi 2014	No	University	Yes	Iran	10 (8/2)	54.0
21	Szabo 2005	Yes	University/hospital	Yes	Belgium, Hungary, Italy, UK	20 (9/11)	52.0
22	Wagner 2012%	Yes	University/hospital	No	Germany	32 (NR)	NR
23	Wiltfang 2003	Yes	University	No	Germany	39 (NR)	46.0
24	Xavier 2014	No	University	Yes	Brazil	15 (8/7)	54.0
	Parallel trials						
25	Calasans-Maia 2013	No	University	-	Brazil	20 (7/13)	44.6
26	Checci 2011	No	University	-	Italy	10 (0/10)	51.0
27	Cordaro 2011	No	University	-	Italy	17 (NR)	42.0
28	de Freitas 2013	No	University	-	Brasil	24 (10/14)	45.1
29	Galindo-Moreno 2011	No	University	-	Spain	28 (18/10)	47.3
30	Hermund 2012	No	University	-	Denmark	20 (9/11)	59.5
31	Jun 2014	No	University	-	Republic of Korea	38 (24/14)	58.2
32	Koch 2010; Stavropoulos 2011	Yes	University	-	Germany	20 (NR)	NR
33	Kuhl 2012; Kuhl 2013	No	University	-	Germany	23 (10/13)	53.0
34	Kurkcu 2012	No	University	-	Turkey	23 (12/11)	48.7
35	Mardas 2010; Mardas 2011; Patel 2013	No	University	-	UK	27 (6/21)	37.3
36	Meijndert 2005 #	No	University	-	Netherlands	10 (5/5)	35.2
37	Meijndert 2008 #	Yes	University/hospital	-	Netherlands	62 (31/31)	33.4
38	Piattelli 2002	No	University	-	Italy	18 (12/6)	49.0
39	Pikdoken 2011	No	Military medical academy	-	Turkey	24 (15/9)	58.9
40	Tosta 2013	No	University	-	Brasil	30 (NR)	NR
41	Wood 2012	No	University	-	USA	33 (13/20)	56.7

M, male; F, female; yrs, years; USA, United States of America; UK, United Kingdom; NR, not reported.
$, some data from ungrafted control group omitted.
%, some data from patients receiving only one graft material are omitted.
#, some data due to inconsistent membrane use omitted.

Appendix 5. Characteristics of the 41 trials included in this systematic review.

Nr	Study	Surgery	Sites	Graft	Membrane	Imps	Insertion time (mos)	Conflict
	Cluster trials							
1	Bettega 2009	SL	36	-AUT (iliac) -AUT (iliac)/PRP/fibrin glue	-Fibrin glue -Fibrin glue+PRP	111	6	Internal
2	Cordaro 2008	SL	47	-XEN (Bio-Oss) -SYN: BCP (BoneCeramic)	Collagen membrane	109	6-8	NR
3	Corinaldesi 2013	SL	18	-XEN (Bio-Oss) -XEN (Bio-Oss)+GF: eptotermin (Osigraf)	Collagen membrane	NR	4	Material donation
4	Crespi 2009a $	ESP	30	-SYN: HA (Sintlife)$ -SYN: CS (Easy Set)	Collagen membrane	NR	3	None
5	Crespi 2009b	SL	30	-AUT (mandible) -SYN: HA (Sintlife)	-	60	5	None
6	Crespi 2011 $	ESP	30	-XEN (Tecnoss)$ -SYN: HA (Sintlife)	Collagen membrane	30	4	NR
7	Felice 2008	VRA	20	-AUT (iliac) -XEN (Bio-Oss)	Collagen membrane	40	4	Material donation
8	Froum 2002 $	ESP	20	-ALL$ -SYN: BG (Biogran)	-	20	6-8	Commercial support
9	Froum 2004 $	ESP	20	-XEN (Osteograf R/N300) -SYN: HA (Osteograf R/LD)	ADMA or e-PTFE membrane	20	6-8	Commercial support
10	Froum 2008	SL	24	-XEN (Bio-Oss) -SYN: BCP (BoneCeramic)	Collagen membrane	NR	6-8	Commercial support
11	Garlini 2014	SL	10	-XEN (Bio-Oss) -SYN: HA (Algipore)	Collagen membrane	14	6-8	None
12	Gholami 2012	ESP	24	-SYN: HA (NanoBone) -SYN: HA (Algipore)	Collagen membrane	24	6-8	NR
13	Kotsakis 2014 $	ESP	24	-XEN (Bio-Oss)+collagen plug -SYN: CP (NovaBone)	-	16	5-6	Material donation & external grant
14	Lee 2008	SL	52	-AUT (misc)+allograft (Puros) -AUT (misc)+xenograft (Bio-Oss) -AUT (misc)+SYN: FHA (C Graft)	-	97	4-9	None
15	Molly 2008 $	ESP	36	-XEN (Bio-Oss) -SYN: PLG (Fisiograft) -SYN: HA (Biocoral)	e-PTFE membrane	NR	6	Commercial support
16	Mordenfeld 2014	LRA	28	-AUT (mandible) 10%+xenograft (Bio-Oss) 90% -AUT (mandible) 60%+xenograft (Bio-Oss) 40%	Collagen membrane	71	8.1	Material donation
17	Raghoebar 2005	SL	10	-AUT (iliac) -AUT (iliac)+PRP	-	30	3	NR
18	Rickert 2011	SL	24	-XEN (Bio-Oss)+stem cells -AUT (mandible)+xenograft (Bio-Oss)	Collagen membrane	NR	3-4	Technical assistance from company
19	Schmitt 2013	SL	45	-AUT (mandible) -ALL (Puros) -XEN (Bio-Oss) -SYN: BCP (BoneCeramic)	Collagen membrane	94	5	NR
20	Shirmohammadi 2014	SL	20	-XEN (Bio-Oss)+autograft 20% (misc) -SYN: HA (Ostim)+autograft 20% (misc)	Collagen membrane			None
21	Szabo 2005	SL/LRA	40/10	-AUT (iliac) -SYN: b-TCP (Cerasorb)	-	80	6	NR
22	Wagner 2012 %	SL	64	-AUT (jaws)+xenograft (Bio-Oss) -SYN: MBCP (Tricos)	-	NR	6	Commercial support
23	Wiltfang 2003	SL	45	-SYN: b-TCP (Curasan)+PRP -SYN: b-TCP (Curasan)	-	NR	6	NR
24	Xavier 2014	SL	30	-ALL (FDBA) -AUT (ramus)	Collagen membrane	80	6	NR
	Parallel trials							
25	Calasans-Maia 2013	ESP	20	-XEN (Bio-Oss) -XEN (Osseus)	-	20	6	Commercial support
26	Checci 2011	ESP	10	-SYN: HA (Sintlife) -SYN: HA (Ostim)	Collagen sponge	10	6	None
27	Cordaro 2011	LRA	22	-AUT (mandible) -AUT+xenograft (Bio-Oss)	Collagen membrane	55	4	External grant

28	de Freitas 2013	LRA	24	-AUT (mandible) -GF: rhBMP-2/ACS	-	62	6	External / commercial grants
29	Galindo-Moreno 2011	SL	24	-AUT (maxilla) 50%+xenograft (Bio-Oss) 50% -AUT (maxilla) 20%+xenograft (Bio-Oss) 80%	Collagen membrane	NR	6	External grants
30	Hermund 2012	SL	20	-AUT (maxilla)+xenograft (Bio-Oss) -AUT (maxilla)+xenograft (Bio-Oss)+bone cells	Collagen membrane	39	4	Commercial support
31	Jun 2014	SL	32	-AUT (extracted tooth) -XEN (Bio-Oss)	-	38	4	Government grant
32	Koch 2010; Stavropoulos 2011	SL	20	-Autologous+b-TCP -rhGDF-5/b-TCP	-	66	3-4	Commercial support
33	Kuhl 2012; Kuhl 2013	SL	23	-AUT (mandible) -AUT (mandible)+SYN: BCP (BoneCeramic) -AUT (mandible)+SYN: BCP (Cerasorb)	-	-	-	Internal
34	Kurkcu 2012	SL	23	-XEN (BonePlus-xs) -SYN: BCP (BoneCeramic)	-	51	6.5	NR
35	Mardas 2010; Mardas 2011; Patel 2013	ESP	26	-XEN (Bio-Oss) -SYN: BCP (BoneCeramic)	Collagen membrane	-	-	Material donation
36	Meijndert 2005 #	LRA	10	-AUT (chin) -XEN (Bio-Oss)	Collagen membrane	NR	3-6	Commercial support
37	Meijndert 2008 #	ESP	62	-AUT (chin) -XEN (Bio-Oss)	Collagen membrane	NR	3-6	Commercial support
38	Piattelli 2002	ESP	24	-AUT (upper/lower jaw) -XEN (Bio-Oss)	-	24	3-6	External grant
39	Pikdoken 2011	SL	24	-AUT (sinus) 20%+xenograft (NuOss) 80% -XEN (NuOss) 80%	Collagen membrane	NR	4	NR
40	Tosta 2013	SL	30	-AUT (maxilla) -SYN: BCP (BoneCeramic)	Collagen membrane	NR	9	Internal
41	Wood 2012	ESP	33	-ALL (DFDBA) -ALL (FDBA)	Collagen membrane	-	-	Material donation

ADMA, acellular dermal matrix allograft; ALL, allograft; AUT, autograft; BC, bone cyst; BCP, biphasic calcium phosphate; b-TCP, beta-tricalcium phosphate; CS, calcium sulfate; DFDBA, demineralized freeze-dried bone allograft; e-PTFE, expanded polytetrafluoroethylene; ESP, extraction socket preservation; FHA, fluoro-hydroxyapatite; GF, growth factor; HA, hydroxyapatite; LRA, lateral ridge augmentation; MBCP, microporous and macroporous biphasic calcium phosphate; mos, months; NR, not reported; PLG, Poly-Lactide-co-Glycolide polymer; PRP, platelet rich plasma; rhBMP-2/ACS, recombinant human bone morphogenetic protein-2 delivered on an Absorbable Collagen Sponge; rhGDF-5/b-TCP, recombinant human growth/differentiation factor-5 coated onto a β-tricalciumphosphate; SYN, synthetic bone substitute; SL, sinus lift; VRA, vertical ridge augmentation; XEN, xenograft.

Appendix 6. Outcomes reported from the 41 trials included in the systematic review.

Nr	Study	Raw data	Bone outcome (follow-up)	Outcome (follow-up)
	Cluster trials			
1	Bettega 2009	-	Bone height & density (NR mos) Histomorphometry (6 mos)	Implant survival (12 mos post-op)
2	Cordaro 2008	-	Histomorphometry (6-8 mos)	-
3	Corinaldesi 2013	-	Bone height (4 mos) Histomorphometry (4 mos)	-
4	Crespi 2009a $	-	Bone height & density (3 mos) Histomorphometry (3 mos)	-
5	Crespi 2009b	-	Histomorphometry (5 mos) Gene expression profiling (5 mos)	-
6	Crespi 2011 $	-	Histomorphometry (4 mos)	-
7	Felice 2008	-	Bone height (4 mos)	-
8	Froum 2002 $	√	Histomorphometry (6-8 mos)	-
9	Froum 2004 $	√	Histomorphometry (6-8 mos)	-
10	Froum 2008	√	Histomorphometry (6-8 mos)	-
11	Garlini 2014	√	Histomorphometry (6-8 mos)	-
12	Gholami 2012	-	Bone width (6-8 mos) Histomorphometry (6-8 mos)	-
13	Kotsakis 2014 $	-	Bone width & height (5 mos)	Implant primary stability (NR mos) Implant success (20 mos post-op)
14	Lee 2008	√	Histomorphometry (4-9 mos)	-
15	Molly 2008 $	-	Histomorphometry (6 mos)	Insertion torque and mobility of the implants (NR mos)
16	Mordenfeld 2014	-	Bone width (7.5 mos) Histomorphometry (8.1 mos)	Implant failure (11.4 mos post-op)
17	Raghoebar 2005	-	Bone density (3 mos) Histomorphometry (3 mos)	Implant failure (20.2 mos post-op) Implant compications (20.2 mos post-op)
18	Rickert 2011	√	Histomorphometry (3.4 mos)	Implant failure (3 mos post-op)
19	Schmitt 2013	-	Bone height (NR mos) Histomorphometry (5 mos)	-
20	Shirmohammadi 2014	√	Histomorphometry (5 mos) Bone height and density (5 mos)	
21	Szabo 2005	√	Histomorphometry (6 mos)	Implant failure (6 mos post-op)
22	Wagner 2012 %	-	Histomorphometry (6 mos)	Implant stability (12 mos post-op)
23	Wiltfang 2003	-	Histomorphometry (6 mos)	-
24	Xavier 2014	√	Histomorphometry (6 mos)	Implant failure (6 mos post-op)
	Parallel trials			
25	Calasans-Maia 2013	√	Histomorphometry (6 mos)	-
26	Checci 2011	-	Histomorphometry (6 mos)	-
27	Cordaro 2011	-	Bone width (24 mos after imp loading)	-
28	de Freitas 2013	-	Bone width (6 mos)	Implant success (6 mos post-op)
29	Galindo-Moreno 2011	-	Histomorphometry (6 mos)	-
30	Hermund 2012	-	Bone height (4 mos) Histomorphometry (4 mos)	-
31	Jun 2014	-	Bone height & density (4 mos) Sinus membrane thickness (4 mos) Histomorphometry (4 mos)	Implant primary stability(4 mos post-op)
32	Koch 2010; Stavropoulos 2011	-	Histomorphometry (3-4 mos)	-
33	Kuhl 2012; Kuhl 2013	-	Bone density & volume (5 mos)	-
34	Kurkcu 2012	-	Histomorphometry (6.5 mos)	-
35	Mardas 2010; Mardas 2011; Patel 2013	-	Periodontal health of neighbouring teeth (8 mos) Bone width, height, and radioopacity (8 mos) Residual bone defects (NR mos) Resistance of bone to trephination (NR mos)	Peri-implant bone height (12 mos post-loading) Implant failure (12 mos post-loading)
36	Meijndert 2005 #	-	Histomorphometry (3-6 mos) Periodontal health (NR mos)	-
37	Meijndert 2008 #	-	Bone height (21-24 mos post-op) Periodontal health (21-24 mos post-op)	
38	Piattelli 2002	-	Microvessel density (3-6 mos)	-
39	Pikdoken 2011	-	Scintigraphic osteoblastic activity (4 mos) Histomorphometry (4 mos)	-
40	Tosta 2013	-	Histomorphometry (9 mos)	Implant failure (12 mos post-op)
41	Wood 2012	-	Histomorphometry (6-7 mos) Bone width and height	-

mos, monts; NR, not reported.

Appendix 7. Details of the risk of bias assessment for each of the 41 included trials in the systematic review.

Nr	Trial	Sequence generation	Allocation concealment	Blinding of participants, personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
1	Bettega 2009	(+) - "The iliac crest graft was then harvested, and the destination for the two techniques (traditional versus APC) was chosen through a two-element randomization table"	(?) - no mention.	(+) - blinding of the operator not possible; outcome assessment safeguarded.	(+) - "All radiological images were read blindly by a radiologist…..Histologic bone assessment was performed blindly by the histologist."	(+) - No drop-outs or patient losses are reported.	(?) - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	(?) - residual bias cannot be excluded.
2	Calasans-Maia 2013	(+) - unclear randomization; judged that the risk of bias could be classified as low: "The volunteer subjects were randomly assigned to the tests groups using an envelope system distribution provided by the principal investigator."	(+) - same as sequence generation.	(+) - blinding of the operator not possible; outcome assessment safeguarded.	(+) - "…, which were assessed by a single observer blinded to the clinical data".	(+) - No drop-outs or patient losses are reported.	(?) - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	(+) - smoking and systemic diseases covered from the exclusion criteria.
3	Checci 2011	(?) - "At the time of extraction, the patients were randomly assigned to the test group (T) or the control group (C)."	(?) - no mention.	(+) - blinding of the operator not possible; outcome assessment safeguarded.	(+) - "Two evaluators performed the histopathological evaluation blindly, using a light polarized microscope (Nikon Eclipse E800M, Tokyo, Japan),.."	(+) - No drop-outs or patient losses are reported.	(?) - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	(+) - smoking and systemic diseases covered from the exclusion criteria.
4	Cordaro 2008	(?) - randomization unclear (see allocation concealment).	(+) - probably adequate: "The randomization envelope was opened and the patient could be allocated to either the test or control group only after completion of the elevation of the sinus membrane; in cases of bilateral sinus augmentation, each sinus was independently randomized to either the test or control group."	(?) - blinding of the operator not possible; outcome assessment unclear.	(?) - no mention.	(-) - Variation in the number of available samples between groups without accounting for it in the results: "Measurable specimens were available from 14 out of 25 sinuses for the test group (56% of the sites) and in 18 out of 23 sinuses in the control group (81.8% of the sites).	(?) - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	(-) - clustered measurements treated correctly, but effect of smoking not addressed.
5	Cordaro 2011	(+) - "Randomization envelopes were generated by an independent statistician with the blocks method and kept by an administrative employee not involved in the study."	(+) - allocation concealment adequate (same as sequence generation).	(?) - blinding of the operator not possible; outcome assessment unclear.	(?) - no mention.	(+) - No drop-outs or patient losses are reported.	(?) - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	(-) - smoking not taken into account, and no raw data given.

6	Corinaldesi 2013	(?) - randomization unclear: "After the sinus membrane had been dissected and raised, block randomisation was used to designate a test side and a control side for each patient."	(?) - no mention.	(?) - blinding of the operator not possible; outcome assessment unclear.	(?) - no mention.	(+) - No drop-outs or patient losses are reported.	(?) - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	(-) - raw data are given for each patient, but smoking among patients not reported.
7	Crespi 2009a	(-) - quasi-randomization (right/left mouth side): "Fifteen sockets, all on the right side of the mouth, received MHA (Ca10-xMgx(PO4)6(OH)2) in granular form (SintLife, Finceramica) (MHA group); 15 sockets on the left side received xenogenic corticocancellous porcine bone (Tecnoss) (PB group); and 15 unfilled random sockets were considered as control (C) group."	(?) - no mention.	(+) - blinding of the operator not possible; outcome assessment safeguarded.	(+) - "A masked examinermeasured the bone level changes 3months after the tooth extractions (Fig. 2)."	(+) - No drop-outs or patient losses are reported.	(?) - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	(+) - raw data are given for each patient (smoking and systemic diseases covered from the exclusion criteria).
8	Crespi 2009b	(?) - randomization unclear: "According to the split-mouth design, all patients received autologous bone particles harvested from the ascending ramus of the mandible22,23 in a randomly assigned maxillary sinus"	(?) - no mention.	(?) - blinding of the operator not possible; outcome assessment unclear.	(?) - no mention.	(+) - No drop-outs or patient losses are reported.	(-) - It is difficult to judge whether selective reporting is a problem, as no protocol exists. Data not adequately reported to allow processing.	(-) - effect of smoking was not taken into account and no raw data reported.
9	Crespi 2011	(-) - quasi-randomization (right/left mouth side): "Split-mouth treatment was performed: 15 sockets in the right side of the jaw received MHA (Ca10-xMgx[PO4]6[OH]2) available in granule form,† 15 sockets in the left side received CS,‡ and 15 unfilled random sockets were considered the control (C) group"	(?) - no mention.	(?) - blinding of the operator not possible; outcome assessment unclear.	(?) - no mention.	(+) - No drop-outs or patient losses are reported.	(?) - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	(-) - clustered measurements treated as independent and no raw data given.
10	de Freitas 2013	(+) - "Twenty-four small paper cards were consecutively marked as test (n = 12) or control (n = 12), folded and placed in a dark container for allocation concealment."	(+) - "An assistant not involved in the study was then asked to draw one paper from the container."	(+) - blinding of the operator not possible; outcome assessment safeguarded.	(+) - "Radiographic recordings were performed by a masked examiner (RSN)."	(+) - No drop-outs or patient losses are reported.	(?) - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	(+) - smoking and systemic diseases covered from the exclusion criteria.
11	Felice 2008	(+) - "A computer-generated restricted randomisation list was created by an office of the S. Orsola-Malpighi hospital. None of the investigators were aware of the randomisation sequence."	(+) - "The randomised codes were enclosed in sequentially numbered, identical, opaque, sealed envelopes. Envelopes	(+) - blinding of the operator not possible; outcome assessment safeguarded.	(+) - "Two dentists (Dr Fabio Rossi and Dr Gerardo Pellegrino) not involved in the treatment of the patients made all the clinical and	(+) - "...no dropout, exclusion or deviation from the protocol occurred up to the insertion of the final prosthesis."	(+) - "...no dropout, exclusion or deviation from the protocol occurred up to the insertion of the final prosthesis."	(-) - clustered measurements treated correctly with paired t-tests, but effect of smoking not addressed.

			were opened sequentially one day before surgery."		radiographic assessments without knowledge of group allocation, therefore, outcome assessors were blind to these assessments. A biostatistician with expertise in dentistry analysed the data, without knowing the group codes."			
12	Froum 2002	(+) - assumed to be adequate: "Treatment selection was then made randomly from sealed envelopes prepared by a statistician."	(+) - assumed to be adequate (same as sequence generation).	(+) - blinding of the operator not possible; outcome assessment safeguarded.	(+) - "...measurements were performed by an investigator who had no knowledge of the treatment rendered."	(+) - No drop-outs or patient losses are reported.	(?) - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	(+) - raw data are given for each patient including patient's gender (smoking and systemic diseases covered from the exclusion criteria).
13	Froum 2004	(+) - assumed to be adequate: "Treatment selection was then made randomly from sealed envelopes prepared by a statistician."	(+) - assumed to be adequate (same as sequence generation).	(+) - blinding of the operator not possible; outcome assessment safeguarded.	(+) - "The processing and histomorphometric measurements were performed by an investigator who had no knowledge of the treatment rendered."	(+) - No drop-outs or patient losses are reported.	(?) - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	(+) - raw data are given for each patient including patient's gender and membrane use (smoking and systemic diseases covered from the exclusion criteria).
14	Froum 2008	(+) - The sinus membrane was then elevated across the floor and up the medial wall. BCP was placed in one subantral compartment and ABBM was placed in the contralateral subantral compartment, as determined by a computer-generated randomized code."	(?) - no mention.	(?) - blinding of the operator not possible; outcome assessment unclear.	(?) - no mention.	(+) - dropout judged not to be substantial or related to the interventions: "One withdrew for financial reasons, one because of an inability to obtain cores within the study time protocol, and one because of an infection that required re-entry and debridement prior to the time required for core harvesting."	(?) - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	(-) - raw data are given for each patient, but smoking among patients not reported.
15	Galindo-Moreno 2011	(?) - "Patients were randomly assigned to the two groups (n=14 each)..	(?) - no mention.	(+) - blinding of the operator not possible; outcome assessment safeguarded.	(+) - "Histological, histomorphometrical, and immunohistochemical analyses were conducted by an experienced, masked examiner (F.O.)."	(+) - No drop-outs or patient losses are reported.	(?) - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	(-) - smoking not taken into account, and no raw data given.
16	Garlini 2014	(?) - “A randomized clinical study with a split-mouth design”	(?) - no mention.	(?) - blinding of the operator not possible; outcome assessment unclear.	(?) - no mention.	(+) - No drop-outs or patient losses are reported.	(?) - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	(-) - effect of smoking was not taken into account and smoking status not reported in raw data.

17	Gholami 2012	(+) - “Fifteen symmetrical pairs were randomly selected, using a random number table, as one side of the mouth in each patient..”	(?) - no mention.	(+) - blinding of the operator not possible; outcome assessment safeguarded.	(+) - The sections were analyzed by an examiner masked to the type of treatment.”	(+) - 2 missing patients; due to the trial’s design, losses are balanced.	(?) - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	(-) - smoking not taken into account, and no raw data given.
18	Hermund 2012	(+) - "and then the patients were randomly assigned to a control (n = 10) or test group (n = 10) using a blinded draw from a bag containing 20 identical pieces of paper with the group name printed on them"	(?) - no mention.	(+) - blinding of the operator not possible; outcome assessment safeguarded.	(+) - "A single, previously calibrated examiner (NUH), who was blinded to treatment group, evaluated all specimens."	(+) - minor missing samples from some implant positions/judged to be insignificant.	(?) - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	(-) - smoking not taken into account, and no raw data given.
19	Jun 2014	(+) - “The allocation of the participants was done by random sequence generator.”	(?) - no mention.	(+) - blinding of the operator not possible; outcome assessment safeguarded.	(+) - “This measurement was performed by one oral and maxillofacial surgeon who does not know the control/ experimental group.”	(+) - equal number of drop-out for the two groups; judged to be insignificant.	(?) - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	(-) - smoking not taken into account, and no raw data given.
20	Koch 2010; Stavropoulos 2011	(+) - "For sinus floor augmentation, three treatment groups were randomized according to a computer-generated list."	(?) - no mention.	(+) - blinding of the operator not possible; outcome assessment safeguarded.	(+) - "Two experienced evaluators (A. S. and H. T.), blinded with respect to treatment group, examined independently the biopsies..."	(+) - only one patient excluded; judged insignificant.	(?) - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	(-) - smoking not taken into account, and membrane used in some cases; no raw data given.
21	Kotsakis 2014	(?) - randomization not clear, as experimental groups were twice as large than the control group and no description is given: "were allocated to either one of the test groups or the control group according to a randomization list."	(?) - no mention.	(+) - blinding of the operator not possible; outcome assessment safeguarded.	(+) - "Clinical and radiographic postoperative measurements were recorded at approximately 5 months by the same blinded examiner who had performed the baseline measurements and was not involved in the surgical treatment"	(+) - No drop-outs or patient losses are reported.	(?) - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	(-) - clustered measurements treated as independent and no raw data given.
22	Kuhl 2012; Kuhl 2013	(+) - "Before surgical treatment, patients were randomly enrolled in one of three treatment groups:"	(?) - no mention.	(?) - blinding of the operator not possible; outcome assessment unclear.	(?) - no mention.	(+) - excluded patients evenly distributed among groups.	(?) - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	(+) - smoking and systemic diseases covered from the exclusion criteria.
23	Kurkcu 2012	(-) - semi-randomization: "The patients were randomly allocated to 1 of 2 groups according to admission order."	(?) - no mention.	(?) - blinding of the operator not possible; outcome assessment unclear.	(?) - no mention.	(+) - excluded patients evenly distributed among groups.	(?) - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	(-) - smoking not taken into account, and no raw data given.
24	Lee 2008	(?) - randomization unclear: "Randomization schedules were designed to provide a balanced distribution of graft material in each patient."	(?) - no mention.	(?) - blinding of the operator not possible; outcome assessment unclear.	(?) - no mention.	(-) - Selective random reporting of samples, leading to unequal distribution among groups: "Ten randomly selected bone core samples	(?) - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	(-) - raw data are given for each patient, but smoking among patients not reported.

						were examined"		
25	Mardas 2010; Mardas 2011; Patel 2013	(+) - "The subjects were randomly assigned to the test or the control group by a computergenerated table. A balanced randomly permuted block approach was used to prepare the randomization tables in order to avoid unequal balance between the two treatments. The subjects were randomized according to smoking habits."	(+) - "After completion of the intrasurgical measurements, the randomization envelope was opened and the assigned treatment (test or control) was revealed to the surgeon."	(+) - blinding of the operator not possible; outcome assessment safeguarded.	(+) - "All the periodontal and intrasurgical measurements were made by a single, blinded previously calibrated examiner other than the surgeon, who was also not aware of the treatment assignment (test or control)."	(+) - One patient exclluded after randomization and this was judged to be insignificant: "Two patients were excluded before randomization due to complete loss of the buccal osseous plate following extraction. One patient withdrew from the study before randomization and another who had been assigned to the test group quit the study before implant placement."	(?) - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	(+) - smokers not excluded, but distributed equally between groups.
26	Meijndert 2005	(+) - "A computer software program randomly placed the participating patients into these groups."	(?) - no mention.	(?) - blinding of the operator not possible; outcome assessment unclear.	(?) - no mention.	(+) - No drop-outs or patient losses are reported.	(?) - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	(+) - smoking and systemic diseases covered from the exclusion criteria.
27	Meijndert 2008	(+) - "A computer software program randomly placed the participating patients into one of these groups, using a balancing procedure aimed at an equal distribution of patients over the treatment groups regarding variables that may interfere with the outcome of the study"	(?) - no mention.	(?) - blinding of the operator not possible; outcome assessment unclear.	(?) - no mention.	(+) - 2 samples were excluded/judged to be insignificant.	(?) - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	(+) - smoking and systemic diseases covered from the exclusion criteria.
28	Molly 2008	(-) - "the experimental treatments, consisting of at least two bone biomaterials and one control, were applied randomly in each subject": randomization unclear, but the paper is titled "Case series".	(?) - no mention.	(?) - blinding of the operator not possible; outcome assessment unclear.	(?) - no mention.	(+) - No drop-outs or patient losses are reported.	(?) - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	(-) - clustered measurements treated correctly with linear mixed modelling, but not clearly reported and no raw data given.
29	Mordenfeld 2014	(+) - probably adequate: "The allocation sequence was computer-generated by a statistician at Gavleborg County Hospital, Sweden, and concealed in envelopes until randomization."	(+) - probably adequate (same as sequence generation).	(?) - blinding of the operator not possible; outcome assessment unclear.	(?) - no mention.	(+) - "All 28 specimens, 14 from each mixture and grafted site, could be used for histomorphometry, and the grafted tissue was easily distinguished from the residual bone."	(?) - It is difficult to judge whether selective reporting is a problem, as the trial was not registered and no protocol exists.	(+) - clustered measurements treated correctly with regression modelling (smoking and systemic diseases covered from the exclusion criteria).
30	Piattelli 2002	(?) - "The defects were filled in a random manner with autologous bone harvested with a trephine from adjacent areas and ground in a bone	(?) - no mention.	(?) - blinding of the operator not possible; outcome assessment unclear.	(?) - no mention.	(+) - No drop-outs or patient losses are reported.	(?) - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	(?) - no mention of smoking as an inclusion/exclusion criterion.

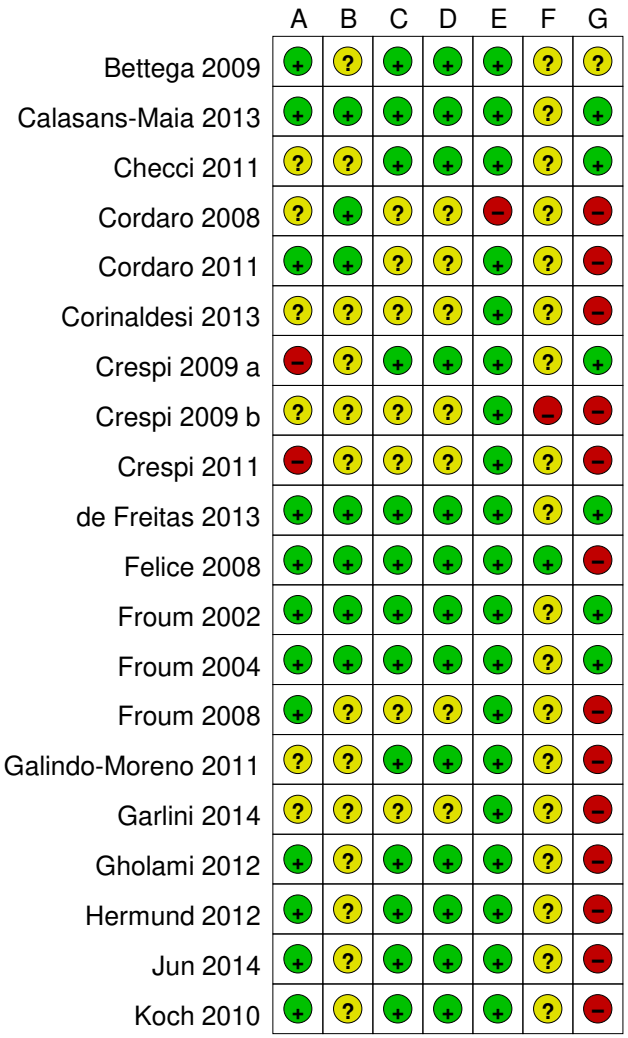
		mill, or with Bio-Oss."						
31	Pikdoken 2011	(?) - randomization unclear: "A balanced randomization was performed by a clinician who intended to distribute the patients into 2 groups including equal numbers of patients."	(?) - no mention.	(+) - blinding of the operator not possible; outcome assessment safeguarded.	(+) - "Histologic and histomorphometric assessments were carried out by 2 pathologists (Z.K. and E.B.) who were not informed about the treatment modalities."	(+) - No drop-outs or patient losses are reported.	(?) - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	(+) - smoking and systemic diseases covered from the exclusion criteria.
32	Raghoebar 2005	(?) - randomization unclear: "Randomly, one side was reconstructed with autologous bone mixed with PRP gel and one side with autologous bone only."	(?) - no mention.	(+) - blinding of the operator not possible; outcome assessment safeguarded.	(+) - "The investigators were blinded for both the clinical and laboratory investigations with regard to the PRP-treated side."	(+) - No drop-outs or patient losses are reported.	(?) - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	(-) - raw data are given for each patient, but no mention of smoking as an inclusion/exclusion criterion.
33	Rickert 2011	(+) - randomization somewhat unclear, but judged to be adequate: "Randomly, performed by envelopes, on one side the augmentation procedure was performed with bovine bone mineral (BioOsss, Geistlich Biomaterials, Wolhusen, Switzerland) seeded with MSCs harvested"	(+) - no mention if the envelopes were opaque and sequentially-numbered, but judged to be adequate (same as sequence generation).	(+) - blinding of the operator not possible; outcome assessment safeguarded.	(+) - "The histologists were blinded to the samples' groups throughout the histomorphometrical analysis."	(+) - One patient excluded, but reasoning adequate.	(?) - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	(+) - raw data are given for each patient (smoking and systemic diseases covered from the exclusion criteria).
34	Schmitt 2013	(?) - randomization unclear: "The test groups (ABB, BCP, and MCBA) and the control group (AB) were allocated to the participant's sinus under randomized conditions."	(?) - no mention.	(?) - blinding of the operator not possible; outcome assessment unclear.	(?) - no mention.	(+) - only half of the harvested samples were analyzed. However, as the distribution among the interventions was relatively well-balanced, it was assumed to have no effect on the results (although the authors didn't formally assess this): "Fifty-three bone biopsies were generated from the later implant site; 41 samples were lost during removal or the location of the implant was peripheral to the augmented maxillary sinus."	(?) - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	(-) - clustered measurements treated as independent, smoking not taken into account, and no raw data given.
35	Shirmohammadi 2014	(?) - "After elevation of the sinusmembrane on a random basis, on one side,Ostim(Heraeus Kulzer GmbH and 63450 Hanau, Germany) with 20% autogenous bone graft was used and on the other side Bio-Oss (Geistlich Pharma AG and 6110 Wolhusen, Switzerland)	(?) - no mention.	(+) - blinding of the operator not possible; outcome assessment safeguarded.	(+) - "The histologist (LR) was blinded to the type of the bone grafts used in sinus augmentation."	(+) - One drop-outs or patient losses reported. Due to the split-mouth nature, observations are balanced.	(+) - No serious discrepancies between published report and registration (http://www.irct.ir/searchresult.php?keyword=IRCT201204157128N2&id=7128&number=2&field=a&prt=1&total=1&m=1)	(+) - raw data are given for each patient (smoking and systemic diseases covered from the exclusion criteria).

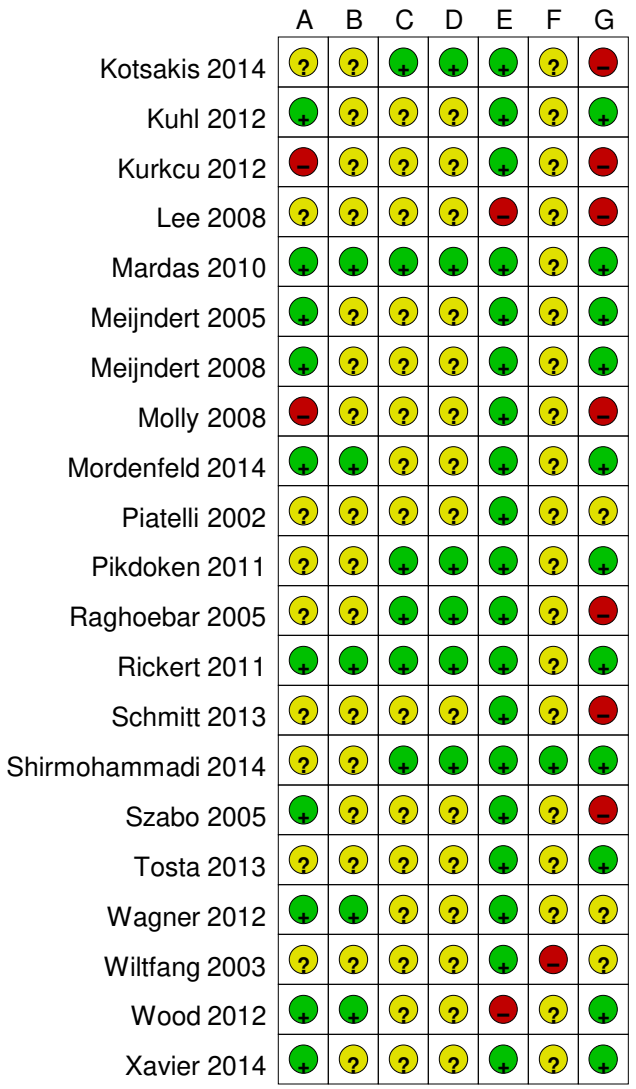
		with 20% autogenous bone graft was applied."						
36	Szabo 2005	(+) - "The choice of sides was randomized using the coin-toss method."	(?) - no mention.	(?) - blinding of the operator not possible; outcome assessment unclear.	(?) - no mention.	(+) - No drop-outs or patient losses are reported.	(?) - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	(-) - raw data are given for each patient (systemic diseases covered from the exclusion criteria). However, no mention of smoking as an inclusion/exclusion criterion.
37	Tosta 2013	(?) - "The space created was grafted – to allow the future placement of implants of 12-mm in length – with either a synthetic particulate bone substitute (test group – biphasic calciumphosphate – Straumann BoneCeramic®, Institut Straumann AG), or with a particulate autogenous bone graft harvested intraorally from the tuberosity area (control group), depending on the randomization process."	(?) - no mention.	(?) - blinding of the operator not possible; outcome assessment unclear.	(?) - no mention.	(+) - No drop-outs or patient losses are reported.	(?) - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	(+) - smoking and systemic diseases covered from the exclusion criteria.
38	Wagner 2012	(+) - somewhat unclear, but judged to be adequate: "Immediately prior to study treatment, the investigator opened a sealed randomization envelope containing the assignment of the MBCP-FS graft treatment to either the right or the left sinus."	(+) - somewhat unclear, but judged to be adequate (same as sequence generation).	(?) - blinding of the operator not possible; outcome assessment unclear.	(?) - no mention.	(+) - No drop-outs or patient losses are reported.	(?) - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	(?) - no mention of smoking as an inclusion/exclusion criterion.
39	Wiltfang 2003	(?) - "One milliliter of PRP was administered in addition to the ceramic material in 17 sites in a randomized prospective study approved by the ethics commission of the University of Erlangen-Nuremberg (application no. 2075)."	(?) - no mention.	(?) - blinding of the operator not possible; outcome assessment unclear.	(?) - no mention.	(+) - No drop-outs or patient losses are reported.	(-) - It is difficult to judge whether selective reporting is a problem, as no protocol exists. Data not adequately reported to allow processing.	(?) - no mention of smoking as an inclusion/exclusion criterion.
40	Wood 2012	(+) - randomization somewhat unclear, but judged to be adequate: "Forty patients were enrolled, and each participant was assigned to one of the two	(+) - allocation concealment somewhat unclear, but judged to be adequate (same as	(?) - blinding of the operator not possible; outcome assessment unclear.	(?) - no mention.	(-) - Thirtytwo out of forty samples analyzed and distribution between experimenal groups not assessed.	(?) - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	(+) - smokers not actively excluded, but no smokers were enrolled.

		treatment groups at the time of surgery by random selection of sealed envelopes."	sequence generation).					
41	Xavier 2014	(+) - randomization somewhat unclear, but judged to be adequate: "The choice of whether the sinus (left or right) would contain the test substance (fresh frozen bone) or autologous bone was determined randomly, using a randomized table."	(?) - no mention.	(?) - blinding of the operator not possible; outcome assessment unclear.	(?) - no mention.	(+) - No drop-outs or patient losses are reported.	(?) - It is difficult to judge whether selective reporting is a problem, as no protocol exists.	(+) - smoking and systemic diseases covered from the exclusion criteria.

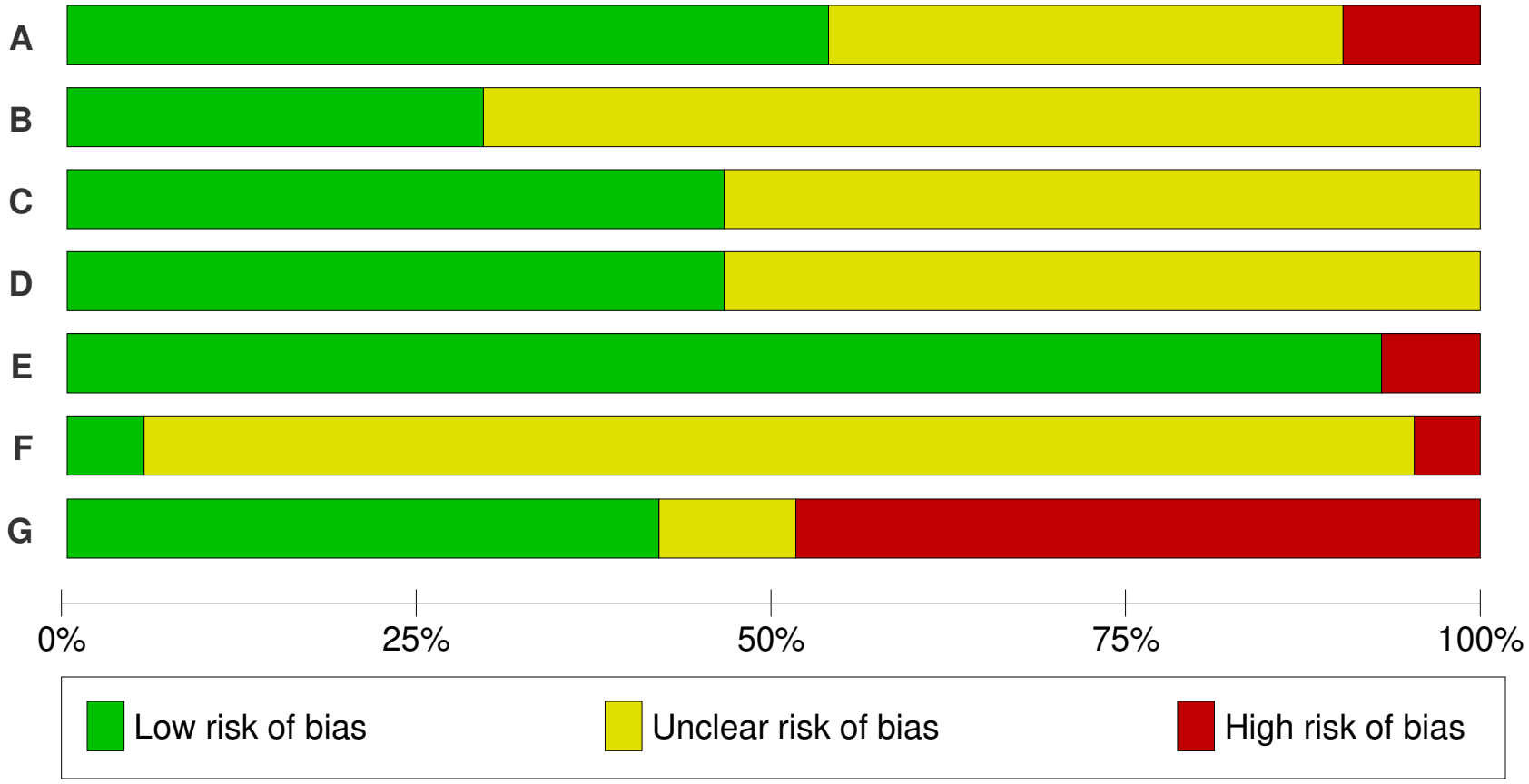
(+), low risk of bias; (-), high risk of bias; (?), unclear risk of bias.

Appendix 8. Risk of bias of the 41 trials included in the systematic review. A, selection bias – random sequence; B, selection bias – allocation; C, performance bias; D, detection bias; E, attrition bias; F, reporting bias; G, other bias.





Appenfix 9. Risk of bias summary across the 41 trials included in the systematic review. A, selection bias – random sequence; B, selection bias – allocation; C, performance bias; D, detection bias; E, attrition bias; F, reporting bias; G, other bias.



Appendix 10. Results of individual trials included in the systematic review, including all reported outcomes. Adjusted estimates stem from individual participant data and are controlled for patient, age, sex, and membrane (where applicable).

Cluster trials – raw and adjusted estimates					
Info	Factor	MD	SE	95% CI	P value
S: Crespi 2009a C: SintLife vs EasySet					
O1: %new bone					
Raw est.	Graft type	-5.02	1.84	-8.62,-1.42	0.006
Adj. est.	Graft type	-5.02	1.84	-8.62,-1.42	0.006
	Age	-0.09	0.09	-0.27,0.09	0.310
	Sex	1.10	2.17	-3.15,5.36	0.611
O2: %residual graft					
Raw est.	Graft type	6.32	1.41	3.56,9.08	<0.001
Adj. est.	Graft type	6.32	1.41	3.56,9.08	<0.001
	Age	-0.09	0.05	-0.19,0.01	0.071
	Sex	0.84	1.20	-1.51,3.19	0.482
O3: %connective tissue					
Raw est.	Graft type	-0.20	2.00	-4.12,3.72	0.920
Adj. est.	Graft type	-0.20	2.00	-4.12,3.72	0.920
	Age	0.10	0.08	-0.06,0.26	0.221
	Sex	1.92	1.91	-1.81,5.65	0.313
O4: bone height change					
Raw est.	Graft type	-2.02	0.17	-2.34,-1.69	<0.001
Adj. est.	Graft type	-2.02	0.17	-2.34,-1.69	<0.001
	Age	-0.01	0.01	-0.03,0.00	0.128
	Sex	0.20	0.20	-0.18,0.59	0.299
S: Froum 2002 C: Biogran vs ALL					
O1: %new bone					
Raw est.	Graft type	-23.28	6.85	-36.69,-9.86	0.001
Adj. est.	Graft type	-25.33	5.99	-37.07,-13.58	<0.001
	Age	-0.58	0.32	-1.20,0.05	0.069
	Sex	1.45	8.48	-15.17,18.08	0.864
	Healing time	6.79	3.98	-1.01,14.59	0.088
O2: %residual graft					
Raw est.	Graft type	8.31	1.73	4.92,11.70	<0.001
Adj. est.	Graft type	9.57	1.62	6.40,12.75	<0.001
	Age	0.07	0.07	-0.07,0.21	0.329
	Sex	-2.08	1.89	-5.79,1.62	0.270
	Healing time	-2.29	0.85	-3.95,-0.63	0.007
O3: %connective tissue					
Raw est.	Graft type	15.65	6.49	2.94,28.37	0.016
Adj. est.	Graft type	17.73	6.14	5.69,29.76	0.004
	Age	0.50	0.33	-0.15,1.15	0.131
	Sex	-0.23	8.85	-17.59,17.12	0.979
	Healing time	-4.17	4.16	-12.33,3.98	0.316
S: Froum 2004 C: Osteograf R/LD vs Osteograf R/N300					
O1: %new bone					
Raw est.	Graft type	2.46	7.70	-12.63,17.55	0.749
Adj. est.	Graft type	4.71	6.61	-8.25,17.68	0.476
	Age	-0.29	0.27	-0.82,0.25	0.290
	Membrane	-13.64	6.65	-26.68,-0.59	0.040
	Healing time	-3.34	4.65	-12.46,5.77	0.472
O2: %residual graft					
Raw est.	Graft type	-5.81	5.01	-15.63,4.01	0.246
Adj. est.	Graft type	-7.99	4.82	-17.43,1.46	0.097
	Age	0.31	0.20	-0.09,0.70	0.128
	Membrane	4.59	5.88	-6.93,16.12	0.435

	Healing time	2.83	3.45	-3.93,9.58	0.412
O3: %connective tissue					
Raw est.	Graft type	7.95	6.76	-5.29,21.19	0.239
Adj. est.	Graft type	7.97	6.85	-5.45,21.38	0.245
	Age	0.23	0.29	-0.33,0.79	0.423
	Membrane	10.12	8.22	-6.00,26.24	0.219
	Healing time	-1.38	4.93	-11.05,8.29	0.780
S: Froum 2008 C: BoneCeramic vs BioOss					
O1: %new bone					
Raw est.	Graft type	6.08	7.08	-7.80,19.97	0.391
Adj. est.	Graft type	4.30	7.28	-9.97,18.57	0.555
	Healing time	5.66	4.75	-3.64,14.97	0.233
O2: %residual graft					
Raw est.	Graft type	1.88	5.53	-8.96,12.73	0.734
Adj. est.	Graft type	3.92	5.35	-6.57,14.41	0.464
	Healing time	-5.99	3.15	-12.16,0.18	0.057
O3: %connective tissue					
Raw est.	Graft type	-8.11	5.04	-18.00,1.77	0.108
Adj. est.	Graft type	-8.22	5.15	-18.31,1.88	0.111
	Healing time	0.26	3.11	-5.85,6.36	0.935
S: Garlini 2014 C: Algipore vs BioOss					
O1: %new bone					
Raw est.	Graft type	-11.18	6.13	-23.20,0.83	0.068
Adj. est.	Graft type	-10.82	6.59	-23.74,2.10	0.101
	Age	0.51	0.22	0.08,0.94	0.021
	Sex	13.32	5.52	2.51,24.12	0.016
	Healing time	-1.82	4.55	-10.73,7.10	0.690
O2: %residual graft					
Raw est.	Graft type	20.56	7.58	5.71,35.42	0.007
Adj. est.	Graft type	23.34	3.23	17.01,29.68	<0.001
	Age	-0.82	0.37	-1.55,-0.10	0.027
	Sex	-9.81	8.95	-27.35,7.72	0.273
	Healing time	-13.89	3.12	-20.00,-7.78	<0.001
O3: %connective tissue					
Raw est.	Graft type	-9.38	5.71	-20.57,1.81	0.100
Adj. est.	Graft type	-9.25	5.95	-20.90,2.40	0.120
	Age	-0.07	0.09	-0.24,0.11	0.451
	Sex	7.02	2.26	2.59,11.45	0.002
	Healing time	-0.68	2.20	-5.00,3.62	0.758
S: Kotsakis 2014 C: NovaBone vs BioOss					
O1: absolute horizontal bone change					
Raw est.	Graft type	-0.13	0.20	-0.52,0.27	0.530
O2: absolute vertical bone change					
Raw est.	Graft type	-0.06	0.11	-0.27,0.15	0.562
S: Rickert 2011 C: BioOss+stem cells vs BioOss+AUT					
O1: %new bone					
Raw est.	Graft type	5.78	1.83	2.19,9.37	0.002
O2: %residual graft					
Raw est.	Graft type	3.18	3.51	-3.69,10.06	0.364
O3: %connective tissue					
Raw est.	Graft type	-1.66	2.49	-6.54,3.21	0.503

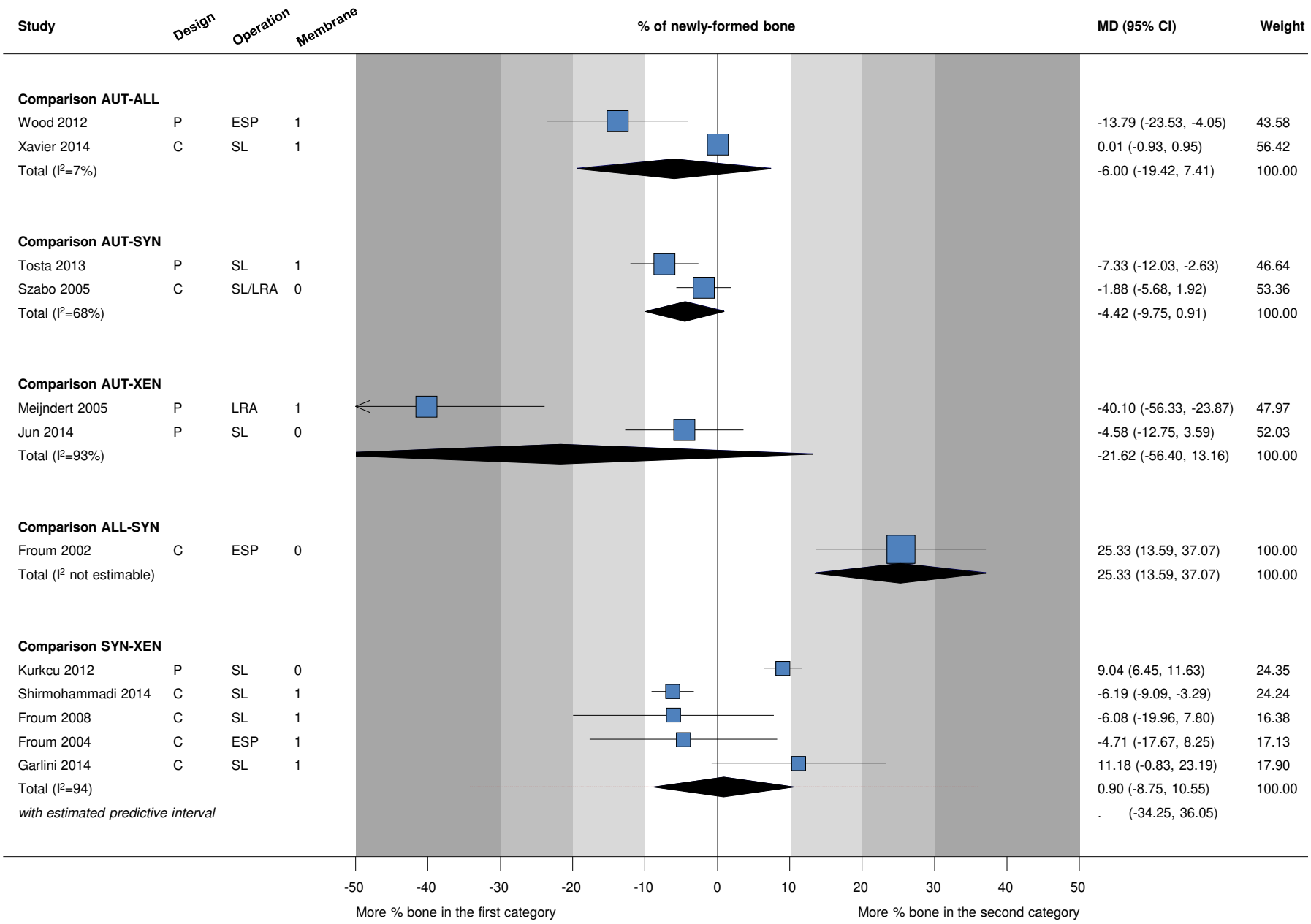
S: Shirmohammadi 2014 C: Ostim vs BioOss					
O1: %new bone					
Raw est.	Graft type	6.19	1.48	3.29,9.09	<0.001
O2: %residual graft					
Raw est.	Graft type	-9.96	2.32	-14.51,-5.41	<0.001
O3: %connective tissue					
Raw est.	Graft type	3.78	3.25	-2.59,10.14	0.245
O4: bone density					
Raw est.	Graft type	22.00	8.00	6.32,37.68	0.006
O5: bone height					
Raw est.	Graft type	0.52	0.35	-0.17,1.21	0.138
S: SzabO2005 C: Cerasorb vs AUT					
O1: %new bone					
Raw est.	Graft type	-1.88	1.94	-5.69,1.93	0.333
O2: %residual graft					
Raw est.	Graft type	5.50	1.01	3.52,7.48	<0.001
O3: %connective tissue					
Raw est.	Graft type	-3.61	1.91	-7.36,0.13	0.059
S: Xavier 2014 C: AUT vs ALL					
O1: %new bone					
Raw est.	Graft type	-0.01	0.48	-0.95,0.93	0.981
O2: %residual graft					
Raw est.	Graft type	-1.16	2.57	-6.20,3.89	0.653
O3: %connective tissue					
Raw est.	Graft type	1.17	2.59	-3.92,6.25	0.653
Parallel trials – Raw estimates – MD (unless stated otherwise)					
S: Calasans-Maia 2013 C: Osseus vs BioOss					
	Graft type				
O1: %new bone		14.4	7.49	-0.28,29.08	0.055
O2: %residual graft		-11.9	5.70	-23.07,-0.73	0.037
O3: %connective tissue		-17.6	5.27	-27.93,-7.27	0.001
O4: bone width change		-0.10	0.06	-0.23,0.03	0.130
S: Checci 2011 C: SintLife vs Ostim					
	Graft type				
O1: %new bone		5.00	15.92	-26.21,36.21	0.754
O2: %residual graft		-6.00	4.43	-14.68,2.68	0.175
O3: %connective tissue		-4.00	4.60	-13.02,5.02	0.385
S: CordarO2011 C: AUT vs BioOss+AUT					
	Graft type				
O1: final bone gain		0.26	0.53	-0.77,1.29	0.622
O2: final bone resorption		-0.64	0.55	-1.72,0.44	0.243
S: de Freitas 2013 C: rhBMP-2/ACS vs AUT					
	Graft type				
O1: clin. bone width		-0.50	0.48	-1.44,0.44	0.298
O2: rad. bone width 2mm from crest		1.00	0.33	0.36,1.65	0.002
O3: rad. bone width 6mm from crest		0.00	0.35	-0.68,0.68	1.00
O4: rad. bone width 10mm from crest		-0.100	0.41	-0.90,0.70	0.807
O5: implant failure (primary stability)		RR:6.56	1.04	0.89,50.23	0.070
S: Galindo-MorenO2011					

C: BioOss+AUT(8/2) vs BioOss+AUT (5/5)					
	Graft type				
O1: %vital bone		1.38	5.30	-9.02,11.78	0.795
O2: %residual graft		11.39	6.30	-0.95,23.73	0.070
O3: %non-mineralized tissue		-12.88	5.61	-23.87,-1.89	0.022
O4: osteoblast cells		-84.84	61.10	-204.59,34.91	0.165
O5: osteoclast cells		-55.97	47.14	-148.37,36.43	0.235
O6: osteocytes		-412.77	164.82	-735.80,-89.74	0.012
O7: osteoid lines		-9.04	3.36	-15.62,-2.46	0.007
S: Hermund 2012 C: BioOss+autograft+bone cells vs BioOss+autograft					
	Graft type				
O1: bone density at position 1		5.00	8.17	-11.01,21.01	0.540
O2: bone density at position 2		5.00	7.43	-9.56,19.56	0.501
O3: bone density at position 3		-11.00	8.42	-27.51,5.51	0.192
S: Jun 2014 C: BioOss vs AUT					
	Graft type				
O1: %new bone		-4.58	4.17	-12.76,3.60	0.272
O2: %residual graft		2.12	4.91	-7.51,11.75	0.666
O3: %connective tissue		2.45	6.69	-10.66,15.56	0.714
O4: osteoid thickness		-4.77	1.72	-8.14,-1.40	0.006
O5: new bone radioopacity (HU)		-51.23	38.36	-126.42,23.96	0.182
O6: new bone mineral density		-0.02	0.01	-0.03,-0.01	0.005
O7: trabecular thickness		-0.01	0.01	-0.02,0.00	0.087
O8: (micro-CT) %new bone/total bone		-4.76	3.90	-12.41,2.89	0.222
Koch 2010+following C: rhGDF-5+Ceraver Osteal vs AUT+Ceraver Osteal					
	Graft type				
O1: %new bone		-3.80	7.49	-18.48,10.88	0.612
O2: %bone marrow		12.10	7.58	-2.76,26.96	0.111
O3: %dense fibrous tissue		1.60	11.47	-20.89,24.09	0.889
O4: %residual graft		-9.90	4.37	-18.47,-1.34	0.023
Kuhl 2012; Kuhl 2013 C: AUT vs Cerasorb or BoneCeramic					
O1: bone density	Cerasorb	-23.00	37.01	-95.55,49.55	0.534
	BoneCeramic	-20.00	32.29	-83.29,43.29	0.536
O2: bone volume	Cerasorb	-4.10	3.80	-11.54,3.34	0.280
	BoneCeramic	-0.70	4.29	-9.11,7.71	0.870
C: Cerasorb vs BoneCeramic					
O3: %residual graft		0.10	2.44	-4.69,4.89	0.967
S: Kurkcu 2012 C: BoneCeramic vs BonePlus-xs					
	Graft type				
O1: %new bone		9.04	1.32	6.46,11.62	<0.001
O2: %residual graft		-2.17	1.93	-5.95,1.61	0.261
O3: %connective tissue		-6.87	2.13	-11.04,-2.70	0.001
Mardas 2010+following C: BoneCeramic vs BioOss					
	Graft type				
O1: change in probing depth		0.30	0.16	-0.01,0.61	0.056
O2: change in gingival recession		-0.10	0.06	-0.22,0.02	0.107
O3: change in bone width		1.00	0.39	0.23,1.77	0.011
O4: change in Bbw		-0.30	0.28	-0.84,0.24	0.279
O5: change in L/Pbw		-0.40	0.32	-1.02,0.22	0.206
O6: change in Mbh		-0.60	0.34	-1.27,0.07	0.080
O7: change in Dbh		0.00	0.40	-0.79,0.79	1.00
O8: hard bone tissue after healing		RR:1.00	0.92	0.17,6.07	1.00
O9: implant failure		RR:0.92	0.92	0.15,5.56	0.930
O10: fenestrations around implants		RR:3.00	1.09	0.36,25.21	0.312
O11: pristine defects around implants		RR:1.00	0.59	0.32,3.17	1.000

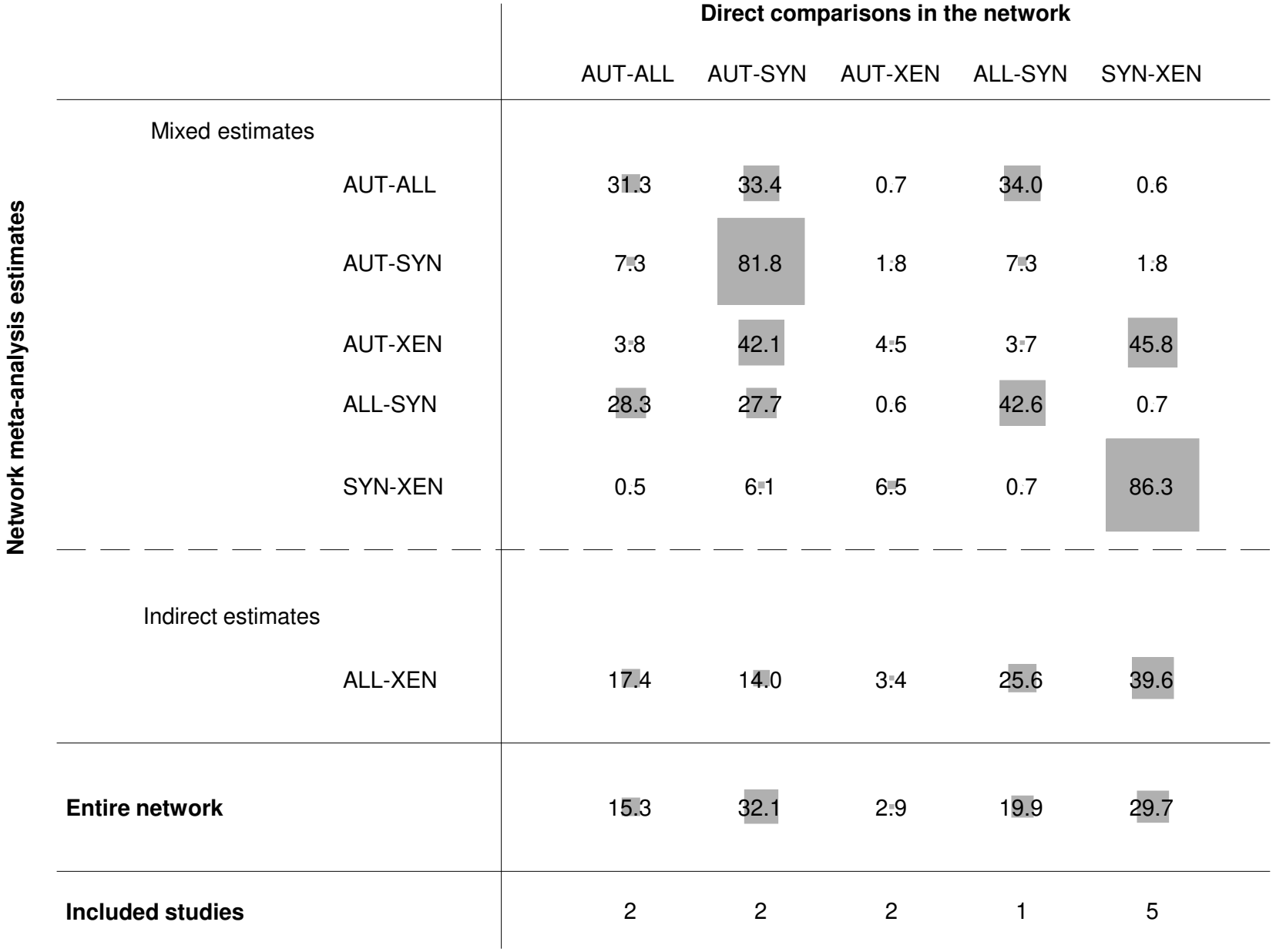
O12: dehiscence around imlpants		RR:0.86	0.86	0.40,1.86	0.696
Various more specific bone height measurements omitted					
S: Meijnert 2005 C: BioOss vs AUT					
	Graft type				
O1: %new bone		-40.10	8.28	-56.32,-23.88	<0.001
O2: %connective tissue		-0.40	7.80	-15.68,14.88	0.959
S: Meijnert 2008 C: BioOss vs AUT					
	Graft type				
O1: bone mesial to implant		-0.03	0.19	-0.40,0.34	0.872
O2: bone distal to implant		-0.03	0.14	-0.30,0.24	0.826
O3: gingiva mesial to implant		0.11	0.12	-0.13,0.35	0.368
O4: gingiva distal to implant		0.16	0.16	-0.15,0.47	0.264
O5: gingiva buccal to implant		-0.21	0.19	-0.58,0.16	0.720
Various measurement at the teeth adjacent to the grafted area omitted					
S: Piatelli 2002 C: BioOss vs AUT					
	Graft type				
O1: microvessel density		-0.10	1.45	-2.94,2.74	0.945
S: Pikdoken 2011 C: BioOss+AUT (8/2) vs BioOss					
	Graft type				
O1: 99mTc-MDP uptake (scintigrafic activity)		0.33	0.40	-0.45,1.11	0.407
O2: %new bone		1.54	0.99	-0.41,3.49	0.121
O3: %residual graft		-2.55	2.95	-8.32,3.22	0.387
O4: %connective tissue		1.18	2.60	-3.91,6.27	0.650
S: Tosta 2013 C: BoneCeramic vs AUT					
	Graft type				
O1: %new bone		-7.33	2.40	-12.04,-2.62	0.002
O2: %connective tissue		-25.82	2.39	-30.51,-21.14	<0.001
S: Wood 2012 C: DFDBA vs FDBA					
	Graft type				
O1: %new bone		13.79	4.97	4.04,23.54	0.006
O2: %residual graft		-16.54	5.33	-26.98,-6.10	0.002
O3: %connective tissue		2.77	3.41	-3.91,9.45	0.416
O4: bone height buccally		-0.20	0.41	-0.99,0.59	0.621
O5: bone height lingually		0.37	0.52	-0.66,1.40	0.480
O6: bone width		0.09	0.59	-1.06,1.24	0.879
O7: %bone width		1.90	5.80	-9.47,13.27	0.743

MD, mean difference; SE, standard error; CI, confidence interval; O, outcome; est., estimate; Adj., adjusted;S, study; C, comparison; ALL, allograft; AUT, autograft; rhBMP-2/ACS, recombinant human bone morphogenetic protein-2 delivered on an Absorbable Collagen Sponge; HU, Hounsfield units; CT, computed tomography; rhGDF-5, recombinant human growth/differentiation factor-5; Bbw, buccal bone width; Pbw, palatal bone width; Mbh, mesial bone height; Dbh, distal bone height; 99mTc-MDP, 99mTc-methylene diphosphonate; DFDBA, demineralized freeze-dried bone allograft; FDBA, mineralized freeze-dried bone allograft.

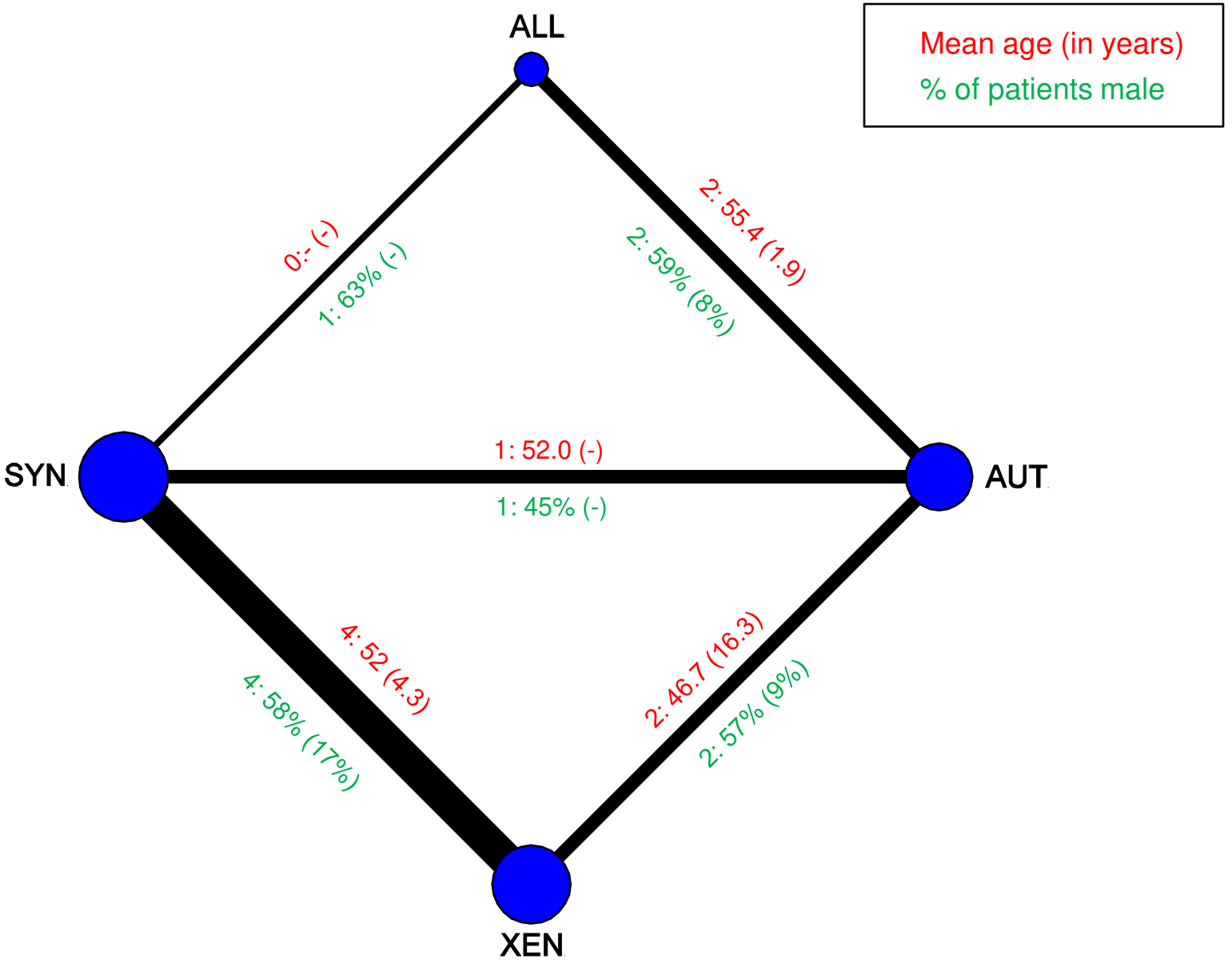
Appendix 11. Direct comparisons from the primary outcome network (mean differences and 95% confidence intervals). MD, mean difference; CI, confidence interval; P, parallel; ESP, extraction socket preservation; C, cluster; SL, sinus lift; LRA, lateral ridge augmentation; AUT, autograft; ALL, allograft; SYN, synthetic bone graft; XEN, xenograft.



Appendix 12. Contribution plot of each direct comparison to the evidence network. AUT, autograft; ALL, allograft; SYN, synthetic bone graft; XEN, xenograft.



Appendix 13. Evaluation of transitivity across network in terms of similarities across comparisons. Presented are the mean patient ages (in years) and the mean sex distribution across the studies included in each comparison in the format: *number of trials with provided data: mean (standard deviation)*

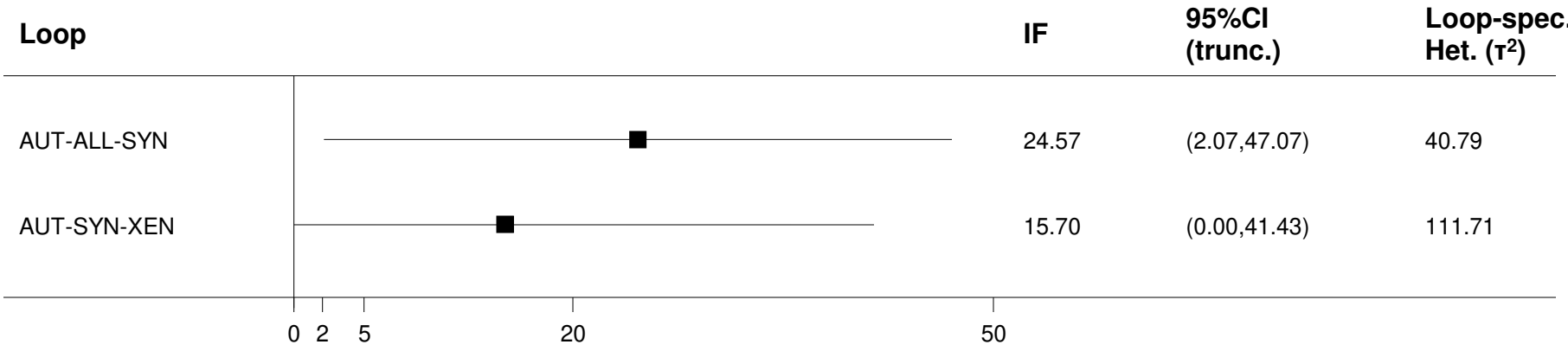


Appendix 14. League table with all direct (white) and mixed (light blue) comparisons from the primary outcome network (mean differences and 95% confidence intervals).

AUT	-13.51 (-28.26,1.24)	-5.50 (-17.42,6.41)	-8.62 (-21.53,4.28)
-6.00 (-19.42,7.41)	ALL	8.01 (-8.57,24.59)	4.89 (-13.05,22.82)
-4.42 (-9.75,0.91)	25.33 (13.59,37.07)	SYN	-3.12 (-13.34,7.10)
-21.62 (-56.40,13.16)	-	0.90 (-8.75,10.55)	XEN

AUT, autograft; ALL, allograft; SYN, synthetic bone graft; XEN, xenograft.

Appendix 15. Evaluation of inconsistency using loop-specific heterogeneity estimates. IF, inconsistency factor; SE, standard error; CI, confidence interval; AUT, autograft; ALL, allograft; SYN, synthetic bone graft; XEN, xenograft.



Loop	IF	SE for IF	z	P value	95% CI	Loop-specific tau^2
AUT-ALL-SYN	24.57	11.48	2.14	0.032	2.07,47.07	40.79
AUT-SYN-XEN	15.70	13.13	1.20	0.232	0.00, 41.43	111.71

Appendix 16. Node-splitting analysis of direct and indirect comparisons.

	Direct		Indirect		Difference		
Side	**MD**	**SE**	**MD**	**SE**	**MD**	**SE**	**P**
AUT-ALL	-6.15	7.55	-33.63	12.91	27.48	14.95	0.066
AUT-SYN	-4.59	9.16	-6.48	9.11	1.89	12.92	0.884
AUT-XEN	-19.60	9.07	1.57	8.55	-21.16	12.49	0.090
ALL-SYN	25.21	11.76	-3.55	9.47	28.76	15.11	0.057
SYN-XEN	0.83	5.43	-20.15	11.51	20.97	12.71	0.099

MD, mean difference; SE, standard error; AUT, autograft; ALL, allograft; SYN, synthetic bone graft; XEN, xenograft.

Appendix 17. Results of the original analysis and of network meta-regressions including possible confounders (using the ML method instead of the original REML one). Factors with considerable effects were re-analyzed with the original REML method and treatment rankings adjusted for this covariate were calculated.

				Subgroup analysis			**Sensitivity analysis**		
		Original		**Surgery type**	**Membrane use**		**Inconsistency model**	**Cluster/parallel design**	**Trial size**
	RLRT	76.15		49.61	0.000		53.03	10.45	43.41
	P value	0.001		0.000	1.000		0.000	0.001	0.000
Explorative comparisons		Ranking			Ranking				
	% new bone	AUT			XEN		-	-	-
		SYN		-	AUT		-	-	-
		XEN		-	SYN		-	-	-
		ALL		-	ALL		-	-	-
	% residual graft	XEN		-	*Same*		-	-	-
		AUT		-			-	-	-
		SYN		-			-	-	-
		ALL		-			-	-	-
	% connective tissue	AUT		-	*Same*		-	-	-
		ALL		-			-	-	-
		XEN		-			-	-	-
		SYN		-			-	-	-

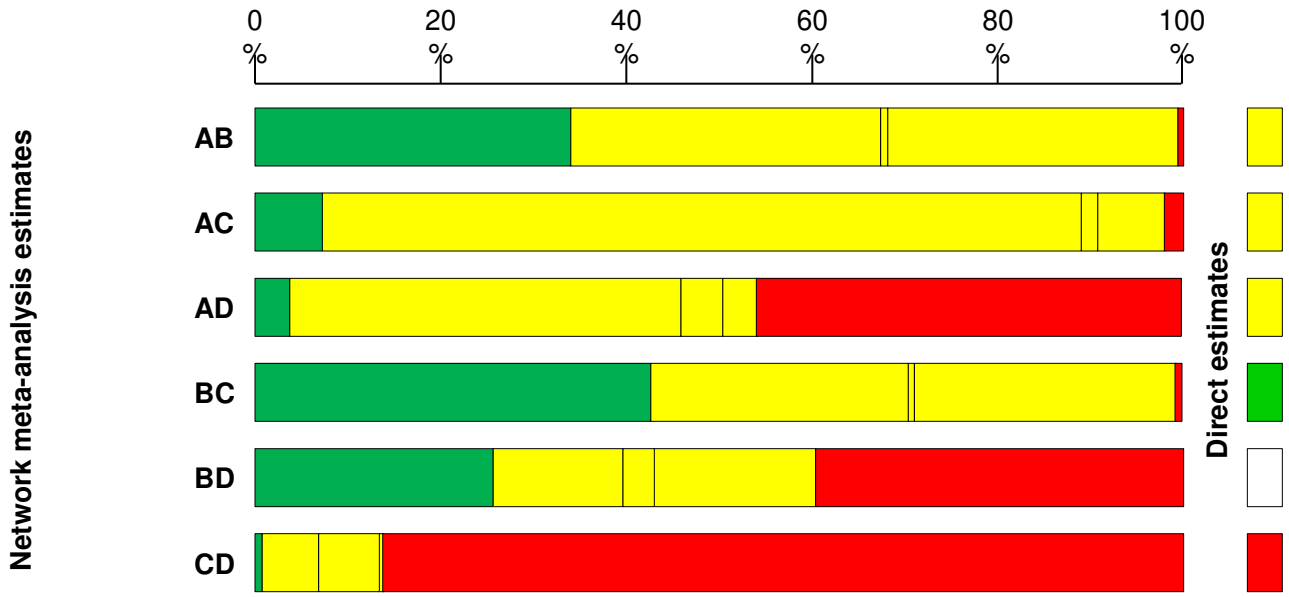
ML, maximum likelihood; REML, restricted maximum likelihood; RLRT, restricted likelihood ratio testing; AUT, autograft; ALL, allograft; SYN, synthetic bone graft; XEN, xenograft.

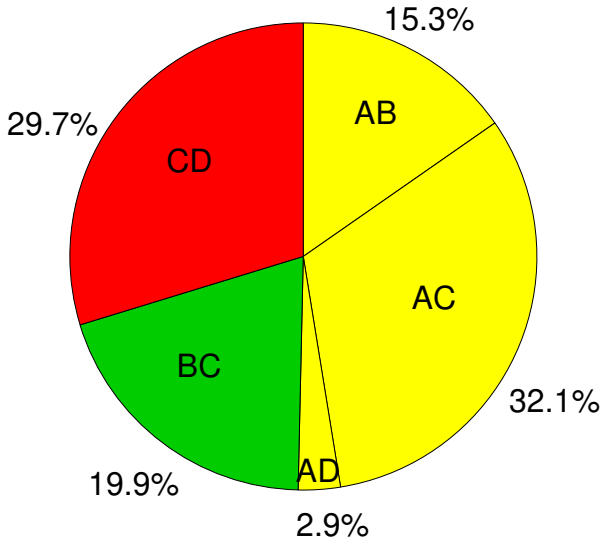
Appendix 18. Details for the GRADE assessment for each pairwise comparison and the evidence network.

Comparison	Study limitations	Indirectness	Inconsistency	Imprecision	Publication bias
AB	No downgrade; less than 10% in high risk of bias	No robust reason to downgrade	Node-splitting yielded an almost statistically significant difference between direct and indirect estimates, which influenced however their magnitude, but not their direction; additionally, no source of heterogeneity was identified through network meta-regression; decided not to downgrade	Downgrade for imprecision; predictive intervals for treatment effect include effects that would have different interpretations	No robust reason to downgrade
AC	No downgrade; less than 10% in high risk of bias	No robust reason to downgrade	No robust evidence of inconsistency	Downgrade for imprecision; predictive intervals for treatment effect include effects that would have different interpretations	No robust reason to downgrade
AD	Downgraded by two levels; almost half of the evidence in high risk of bias	No robust reason to downgrade	Node-splitting yielded an almost statistically significant difference between direct and indirect estimates, which influenced both their magnitude and their direction; additionally, no source of heterogeneity was identified through network meta-regression; decided to downgrade by one	Downgrade for imprecision; predictive intervals for treatment effect include effects that would have different interpretations	No robust reason to downgrade
BC	No downgrade; less than 10% in high risk of bias	No robust reason to downgrade	Node-splitting yielded an almost statistically significant difference between direct and indirect estimates, which influenced both their magnitude and their direction; additionally, no source of heterogeneity was identified through network meta-regression; decided to downgrade by one	Downgrade for imprecision; predictive intervals for treatment effect include effects that would have different interpretations	No robust reason to downgrade
BD	Downgrade by one level; one third of the evidence in high risk of bias	No robust reason to downgrade	Only indirect evidence available	Downgrade for imprecision; predictive intervals for treatment effect include effects that would have different interpretations	No robust reason to downgrade
CD	Downgraded by two levels; most evidence in high risk of bias	No robust reason to downgrade	Node-splitting yielded an almost statistically significant difference between direct and indirect estimates, which influenced both their magnitude and their direction; additionally, no source of heterogeneity was identified through network meta-regression; decided to downgrade by one	Downgrade for imprecision; predictive intervals for treatment effect include effects that would have different interpretations	No robust reason to downgrade
Ranking	Downgrade by one level; one third of the evidence in high risk of bias	No robust reason to downgrade; membrane use could possibly have a modifying effect, but this was discarded due to lack of credibility	Global Q test for inconsistency was almost statistically significant (P=0.061); however, model fit with the design-by-treatment model was not greatly improved and treatment ranking was relatively robust; decided not to downgrade	No robust reason to downgrade	No robust reason to downgrade

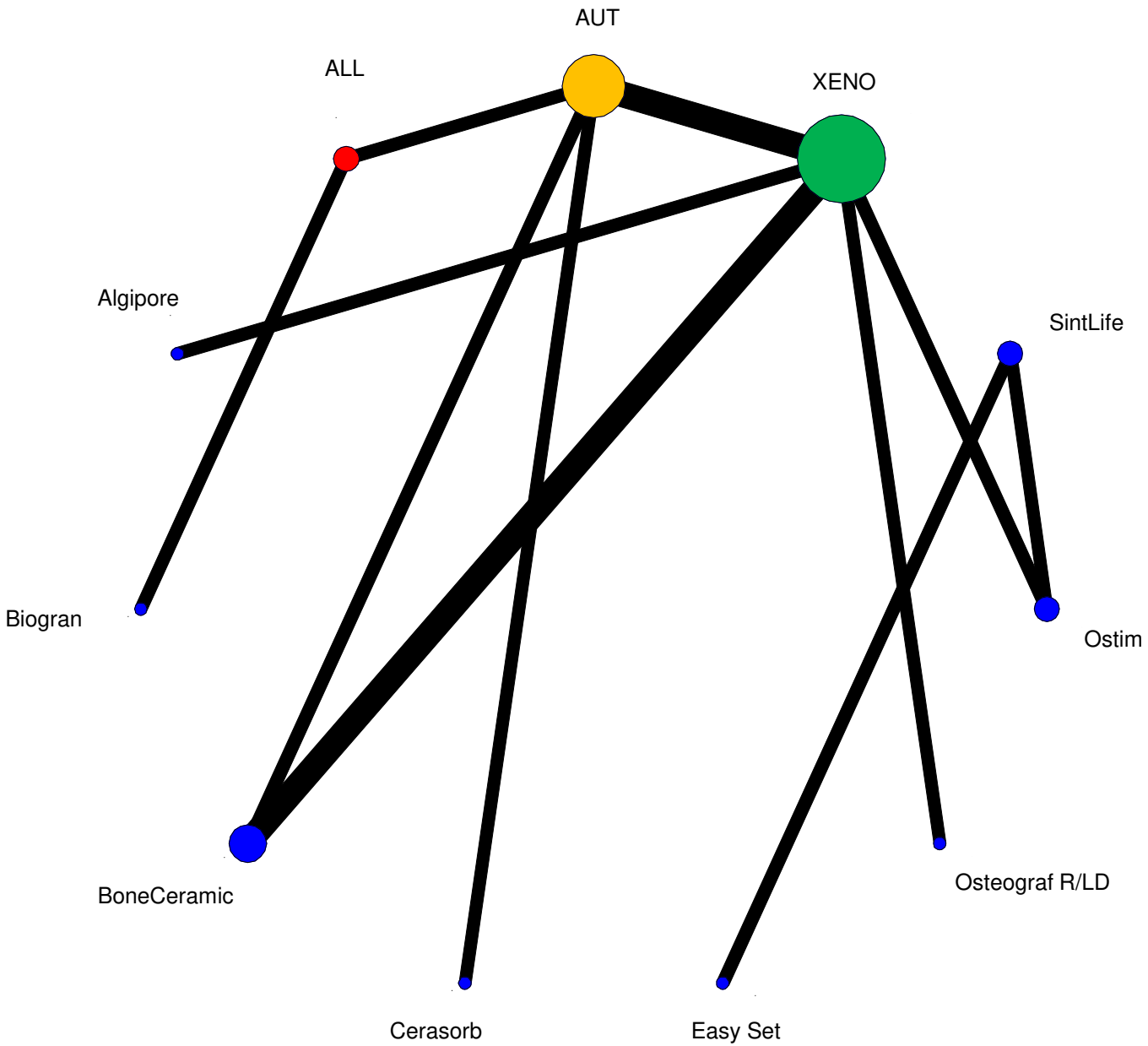
A, autograft; B, alloplast; C, synthetic bone graft; D, xenograft..

Appendix 19. Study limitations for each network estimate for each pairwise comparison and for the whole network of %new bone. A, autograft; B, allograft; C, synthetic bone graft; D, xenograft.

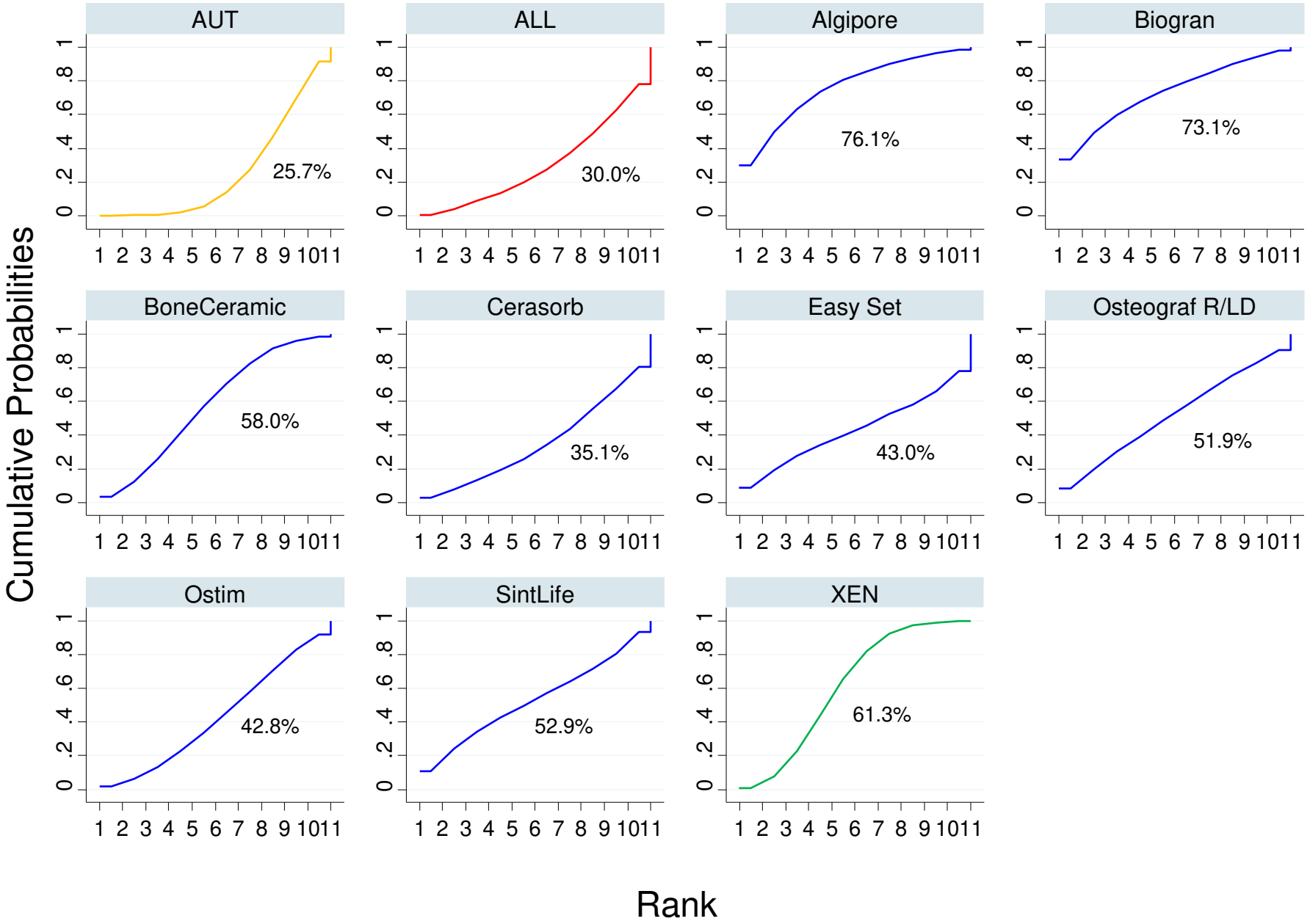




Appendix 20. Alternate network geometry. ALL, allograft; AUT, autograft; XENO, xenolograft.



Appendix 21. Plots of the surface under the cumulative ranking curves for all treatments in the primary outcome alternative network. AUT, autograft; ALL, allograft; XEN, xenograft.



Appendix 22. Investigation of heterogeneity sources: effect of covariates on the % of new bone from individual patient data.

Factor	Comparison	Studies	MD (95% CI)	P	I^2 (95% UI)	95% PrI
Patient age	One yr increase	4	-0.07 (-0.45, 0.31)	0.707	71% (0%,88%)	-1.66,1.52
Patient sex	Male-female	3	4.79 (-3.40,12.98)	0.252	53% (0%,85%)	-81.14,90.72
Healing time	One mo increase	4	2.06 (-3.03,7.15)	0.427	26% (0%,76%)	-13.92,18.04
Membrane type	EPTFE-ADMA	1	-13.64 (-26.67,-0.61)	0.040	-	-

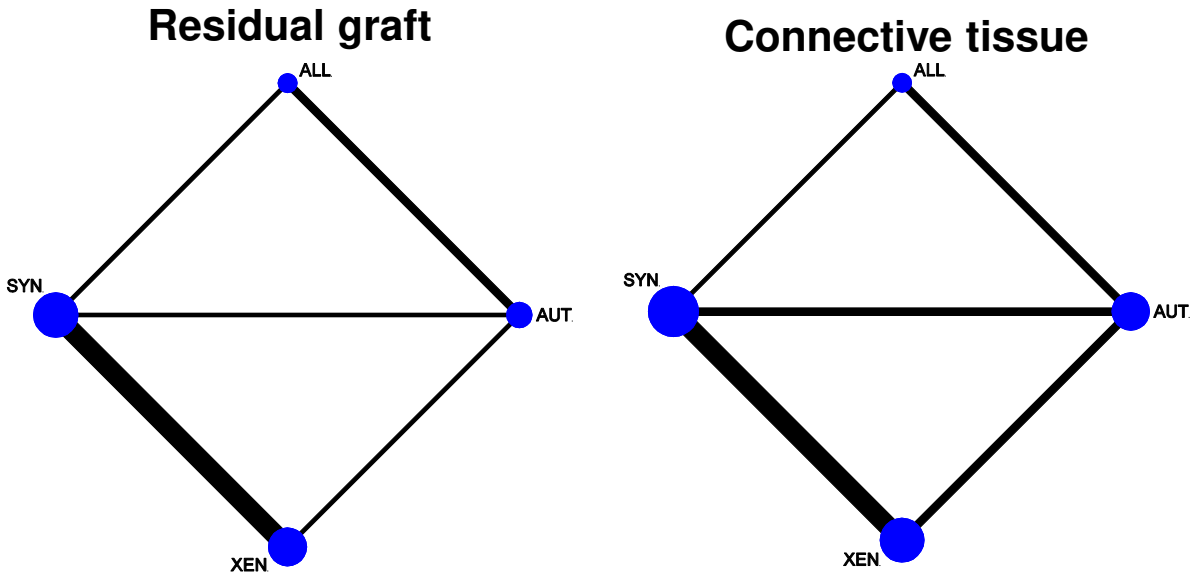
MD, mean difference; CI, confidence interval; UI, uncertainty interval; PrI, predictive interval; EPTFE, expanded polytetrafluoroethylene; ADMA, acellular dermal matrix allograft.

Appendix 23. Direct estimates for the secondary histomorphometric outcomes.

Connective tissue						
Comparison	Studies	MD (95% CI)	I^2 (95% UI)	tau^2	95% PrI	P
AUT-ALL	2	1.76 (-2.29.5.80)	0% (-)	0.00	-	0.395
AUT-SYN	2	14.67 (-7.10,36.43)	98% (-)	241.96	-	0.187
AUT-XEN	2	-1.24 (-11.19,8.71)	0% (-)	0.00	-	0.807
ALL-SYN	1	17.73 (5.70,29.76)	-	0.00	-	0.004
SYN-XEN	5	1.00 (-5.50,7.50)	69% (0%,86%)	34.42	-20.45,22.45	0.763
Residual graft						
AUT-ALL	2	8.14 (-6.87,23.15)	85% (-)	100.77	-	0.288
AUT-SYN	1	5.50 (3.52,7.48)	-	0.00	-	<0.001
AUT-XEN	1	-2.12 (-11.74,7.50)	-	0.00	-	0.666
ALL-SYN	1	-9.57 (-12.75,-6.39)	-	0.00	-	<0.001
SYN-XEN	5	-1.96 (-13.54,9.62)	95% (91%,96%)	160.53	-46.45,9.62	0.740

MD, mean difference; CI, confidence interval; UI, uncertainty interval; PrI, predictive interval; AUT, autograft; ALL, allograft; SYN, synthetic bone graft; XEN, xenograft.

Appendix 24. Network plots and contribution plots for the secondary histomorphometric outcomes. A, AUT (autograft); B, ALL (allograft); C, SYN (synthetic bone graft); D, XEN (xenograft).



Direct comparisons in the network

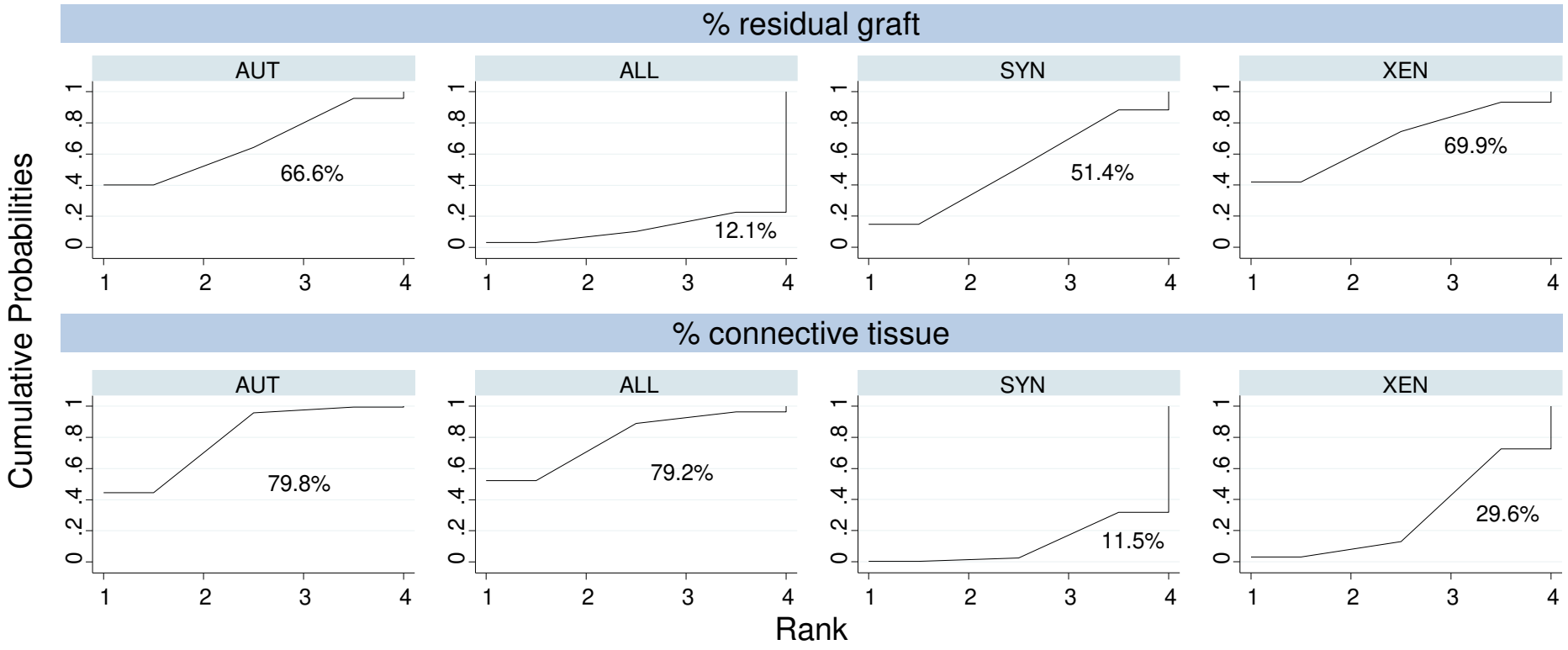
Network meta-analysis estimates	Residual graft					Connective tissue				
	AvsB	AvsC	AvsD	BvsC	CvsD	AvsB	AvsC	AvsD	BvsC	CvsD
Mixed estimates										
AvsB	3.0	47.3	0.8	48.1	0.8	84.9	1.3	4.2	5.5	4.2
AvsC	1.6	93.6	1.6	1.6	1.6	21.7	7.4	24.6	21.6	24.7
AvsD	0.5	28.1	42.5	0.4	28.5	17.1	5.8	37.4	17.0	22.8
BvsC	4.0	4.0	0.1	91.8	0.1	27.5	6.3	21.2	23.8	21.2
CvsD	0.6	35.9	36.5	0.7	26.3	9.4	3.2	12.6	9.4	65.4
Indirect estimates										
BvsD	2.0	21.0	23.0	37.5	16.5	31.5	3.9	27.6	16.5	20.4
Entire network	1.9	35.9	18.8	30.1	13.3	29.6	5.0	22.9	16.8	25.8
Included studies	2	1	1	1	5	2	2	2	1	5

Appendix 25. League table with all mixed comparisons from the primary outcome network (mean differences and 95% confidence intervals.

Residual graft					**Connective tissue**			
AUT	9.23 (-3.85,22.32)	1.73 (-11.13,14.60)	-0.56 (-14.41,13.28)		AUT	-0.51 (-11.54,10.52)	**10.54 (1.33,19.74)**	8.20 (-2.14,18.54)
	ALL	-7.50 (-22.30,7.30)	-9.80 (-26.08,6.48)			ALL	11.05 (-1.62,23.71)	8.71 (-5.16,22.59)
		SYN	-2.30 (-11.36,6.76)				SYN	-2.34 (-10.18,5.51)
			XEN					XEN

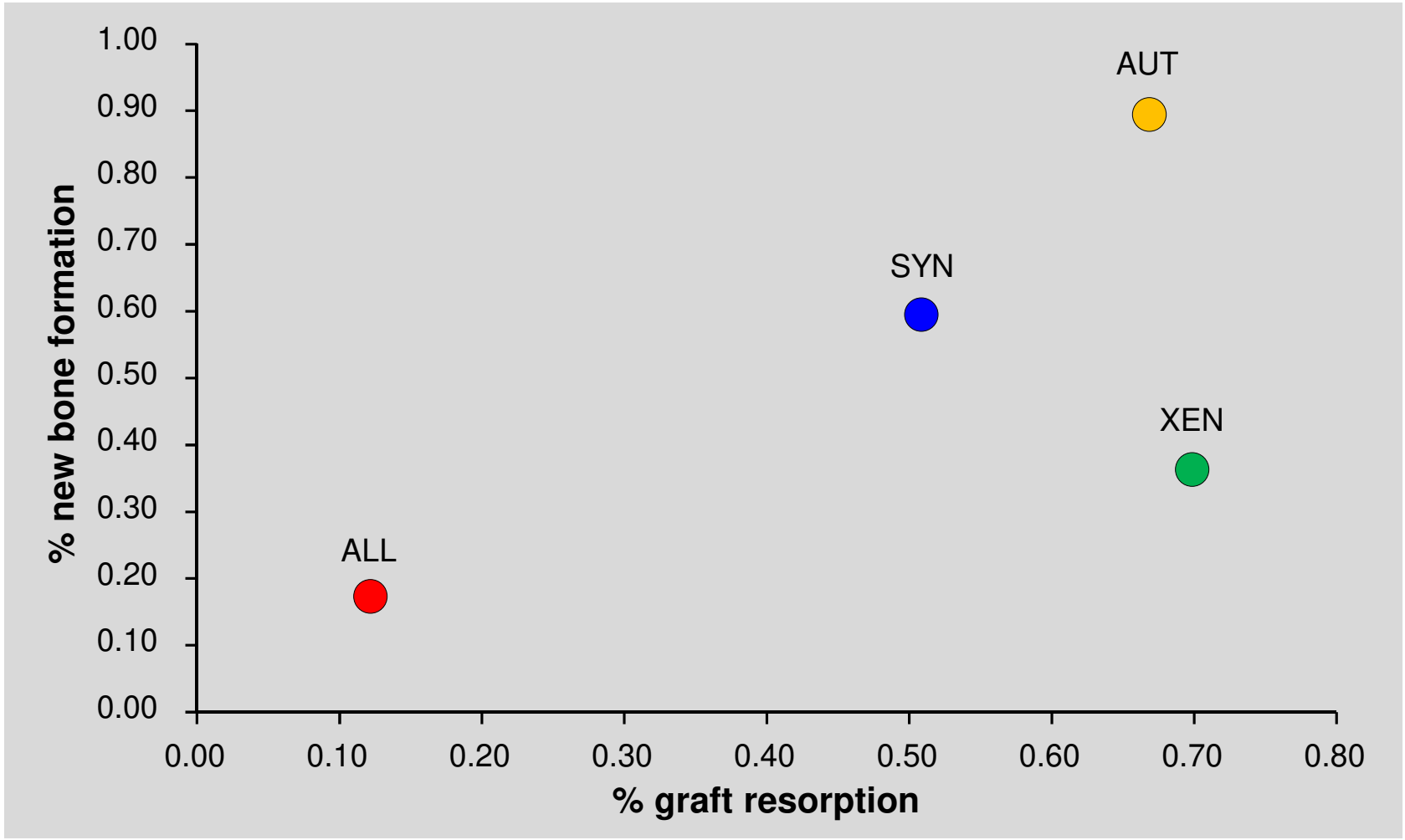
AUT = autograft; ALL = allograft; SYN = synthetic bone graft; XEN = xenograft.

Appendix 26. Ranking of various grafts according to the networks for the secondary histomorphometric outcomes of % residual graft and % connective tissue. AUT, autograft; ALL, allograft; SYN, synthetic bone graft; XEN, xenograft; SUCRA, surface under the cumulative ranking curve.



	% Residual graft				% Connective tissue			
Rank	AUT	ALL	SYN	XEN	AUT	ALL	SYN	XEN
Best	40.4	3.2	14.7	41.9	44.5	52.2	0.3	3.1
Mean rank	2.0	3.6	2.5	1.9	1.6	1.6	3.7	3.1
SUCRA	66.6%	12.1%	51.4%	69.9%	79.8%	79.2%	11.5%	29.6%

Appendix 27. Clustered ranking plot of the graft network based on cluster analysis of SUCRA values for two different outcomes: % new bone and % residual graft. AUT, autograft; SYN, synthetic bone graft; XEN, xenograft; ALL, allograft.



Appendix 28. Node-splitting analysis of direct and indirect comparisons for the secondary histomorphometric outcomes.

	Residual graft								Connective tissue						
	Direct		Indirect		Difference				Direct		Indirect		Difference		
Side	MD	SE	MD	SE	MD	SE	P		MD	SE	MD	SE	MD	SE	P
AUT-ALL	8.25	8.33	11.94	13.61	-3.69	15.97	0.817		1.95	6.62	-8.51	11.83	10.46	13.56	0.440
AUT-SYN	5.50	1.00	-0.77	8.90	6.27	14.15	0.658		14.57	6.32	5.42	7.09	9.15	9.50	0.336
AUT-XEN	-2.12	12.09	0.37	9.53	-2.49	15.39	0.872		-1.13	7.43	15.49	6.32	-16.62	9.76	0.088
ALL-SYN	-9.57	11.18	-5.37	11.64	-4.19	16.14	0.795		17.71	10.78	6.97	8.44	10.74	13.70	0.433
SYN-XEN	-1.97	5.23	-4.86	14.83	2.89	15.72	0.854		0.74	4.01	-16.83	8.96	17.56	9.80	0.073

MD, mean difference; SE, standard error; AUT, autograft; ALL, allograft; SYN, synthetic bone graft; XEN, xenograft .

Appendix 29. Communications with authors of trials.

Nr	Study	Paper	Sent for	Answered
1	Bettega 2009	Bettega G, Brun JP, Boutonnat J, Cracowski JL, Quesada JL, Hegelhofer H, et al. Autologous platelet concentrates for bone graft enhancement in sinus lift procedure. Transfusion 2009;49:779-85.	Data	Awaiting response
2	Cordaro 2008	Cordaro L, Bosshardt DD, Palattella P, Rao W, Serino G, Chiapasco M. Maxillary sinus grafting with Bio-Oss or Straumann Bone Ceramic: histomorphometric results from a randomized controlled multicenter clinical trial. Clin Oral Imp Res 2008;19:796-803.	Data	Awaiting response
3	Corinaldesi 2013	Corinaldesi G, Piersanti L, Piattelli A, Iezzi G, Pieri F, Marchetti C. Augmentation of the floor of the maxillary sinus with recombinant human bone morphogenetic protein-7: a pilot radiological and histological study in humans. Br J Oral Maxillofac Surg 2013;51:247-52.	Data	Awaiting response
4	Crespi 2009a,b,2011	-Crespi R, Cappare P, Gherlone E. Magnesium-enriched hydroxyapatite compared to calcium sulfate in the healing of human extraction sockets: radiographic and histomorphometric evaluation at 3 months. J Periodontol 2009;80:210-8. -Crespi R, Mariani E, Benasciutti E, Cappare P, Cenci S, Gherlone E. Magnesium-enriched hydroxyapatite versus autologous bone in maxillary sinus grafting: combining histomorphometry with osteoblast gene expression profiles ex vivo. J Periodontol 2009;80:586-93. -Crespi R, Cappare P, Gherlone E. Comparison of magnesium-enriched hydroxyapatite and porcine bone in human extraction socket healing: a histologic and histomorphometric evaluation. Int J Oral Maxillofac Imp 2011;26:1057-62.	Data	Awaiting response
5	Felice 2008	Felice P, Marchetti C, Piattelli A, Pellegrino G, Checchi V, Worthington H, et al. Vertical ridge augmentation of the atrophic posterior mandible with interpositional block grafts: bone from the iliac crest versus bovine anorganic bone. Eur J Implantol 2008;1:183-98.	Data	Awaiting response
6	Kotsakis 2014	Kotsakis GA, Salama M, Chrepa V, Hinrichs JE, Gaillard P. A randomized, blinded, controlled clinical study of particulate anorganic bovine bone mineral and calcium phosphosilicate putty bone substitutes for socket preservation. Int J Oral Maxillofac Imp 2014;29:141-51.	Data	Responded; sent raw data
7	Molly 2008	Molly L, Vandromme H, Quirynen M, Schepers E, Adams JL, van Steenberghe D. Bone formation following implantation of bone biomaterials into extraction sites. J Periodontol 2008;79:1108-15.	Data	Awaiting response
8	Mordenfeld 2014	Mordenfeld A, Johansson CB, Albrektsson T, Hallman M. A randomized and controlled clinical trial of two different compositions of deproteinized bovine bone and autogenous bone used for lateral ridge augmentation. Clin Oral Imp Res 2014;25:310-20.	Data	Awaiting response
9	Raghoebar 2005	Raghoebar GM, Schortinghuis J, Liem RS, Ruben JL, van der Wal JE, Vissink A. Does platelet-rich plasma promote remodeling of autologous bone grafts used for augmentation of the maxillary sinus floor? Clin Oral Imp Res 2005;16:349-56.	Data	Awaiting response
10	Schmitt 2013	Schmitt CM, Doering H, Schmidt T, Lutz R, Neukam FW, Schlegel KA. Histological results after maxillary sinus augmentation with Straumann(R) BoneCeramic, Bio-Oss(R), Puros(R), and autologous bone. A randomized controlled clinical trial. Clin Oral Imp Res 2013;24:576-85.	Data	Awaiting response
11	Wagner 2012	Wagner W, Wiltfang J, Pistner H, Yildirim M, Ploder B, Chapman M, et al. Bone formation with a biphasic calcium phosphate combined with fibrin sealant in maxillary sinus floor elevation for delayed dental implant. Clin Oral Imp Res 2012;23:1112-7.	Data	Awaiting response
12	Wiltfang 2003	Wiltfang J, Schlegel KA, Schultze-Mosgau S, Nkenke E, Zimmermann R, Kessler P. Sinus floor augmentation with beta-tricalciumphosphate (beta-TCP): does platelet-rich plasma promote its osseous integration and degradation? Clin Oral Imp Res 2003;14:213-8.	Data	Awaiting response
13	Esposito, Marco	-Cannizzaro G, Felice P, Leone M, Viola P, Esposito M. Early loading of implants in the atrophic posterior maxilla: lateral sinus lift with autogenous bone and Bio-Oss versus crestal mini sinus lift and 8-mm hydroxyapatite-coated implants. A randomised controlled clinical trial. Eur J Oral Implantol 2009;2:25-38. -Cannizzaro G, Felice P, Minciarelli AF, Leone M, Viola P, Esposito M. Early implant loading in the atrophic posterior maxilla: 1-stage lateral versus crestal sinus lift and 8 mm hydroxyapatite-coated implants. A 5-year randomised controlled trial. Eur J Oral Implantol 2013;6:13-25. -Esposito M, Cannizzaro G, Soardi E, Pellegrino G, Pistilli R, Felice P. A 3-year post-loading report of a randomised controlled trial on the rehabilitation of posterior atrophic mandibles: short implants or longer implants in vertically augmented bone? Eur J Oral Implantol 2011;4:301–311. -Esposito M, Cannizzaro G, Soardi E, Pistilli R, Piattelli M, Corvino V, Felice P. Posterior atrophic jaws rehabilitated with prostheses supported by 6 mm-long, 4 mm-wide implants or by longer implants in augmented bone. Preliminary results from a pilot randomised controlled trial. Eur J Oral Implantol 2012;5:19-33. -Esposito M, Piattelli M, Pistilli R, Pellegrino G, Felice P. Sinus lift with guided bone regeneration or anorganic bovine bone: 1-year post-loading results of a pilot randomised clinical trial. Eur J Oral Implantol 2010;3:297-305. -Felice P, Scarano A, Pistilli R, Checchi L, Piattelli M, Pellegrino G, Esposito M. A comparison of two techniques to augment maxillary sinuses using the lateral window approach: rigid synthetic resorbable barriers versus anorganic bovine bone. Five-month post-loading clinical and histological results of a pilot randomised controlled clinical trial. Eur J Oral Implantol 2009;2:293-306.	Papers & data	Responded; sent papers
14	Lee 2008	Lee CY, Rohrer MD, Prasad HS. Immediate loading of the grafted maxillary sinus using platelet rich plasma and autogenous bone: a preliminary study with histologic and histomorphometric analysis. Implant Dent 2008;17:59-73.	Clarification	Awaiting response

Appendix 30. Additional information regarding this systematic review.

Author contributions

SNP conceived the idea and wrote the first draft of the protocol. SNP, PNP, JD, WG revised the protocol. SNP performed the literature searches, extracted search hits, and did screening by title. SNP, PNP, and JD did study selection by abstract and full-text, did data extraction, and assessed the risk of bias in triplicate, while WG resolved any conflicts that arose. SNP handled communications with trialists, performed the statistical analysis (individual patient data processing, pairwise and network meta-analyses), and wrote the first draft of the manuscript. SNP, PNP, JD, and WG assisted in the interpretation of the results and revised the manuscript draft. SNP submitted the manuscript, is the guarantor and responsible for the accuracy of the data and for future updates of the review.

Post hoc changes to the protocol

- Smoking was not tested in the investigation for heterogeneity sources, as during piloting of the literature, strong evidence of impaired wound and bone healing was not found for smoking from re-analysis of raw data and was decided that this did not pertain to uninterrupted physiological graft healing.
- The method of measuring the outcome was not tested in the investigation for heterogeneity sources, as all studies used similar procedures.
- Many secondary outcomes listed in the protocol not pertaining to histomorphometry were not included in the review. Due to the heavy number of reported outcomes, which would make this review difficult to present and read, we focused only on the primary outcome (histomorphometrical %new bone) and the two most often-reported histomorphometrical secondary outcomes from the protocol (%residual graft and %connective tissue). All outcomes however reported from include trials are analyzed and reported in Appendix 10.
- We had planned to restrict analyses to studies with use of membrane and a minimum of 4 months of uninterrupted healing. As however no differences were found for membrane use from our analyses and all studies had 6 or more months of healing, this was discarded.

Appendix References

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Higgins JP, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Research Synthesis Methods* 2012;**3:**98–110.

Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Statistics in Medicine* 2010;**29:**932–944.